



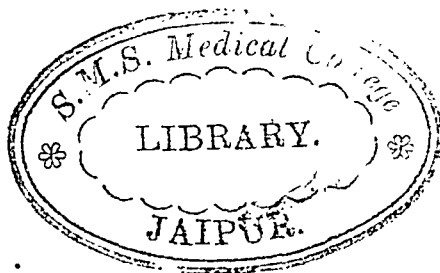
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EDITED BY  
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ORIGINAL ARTICLES.

THE RETAINED GALL-BLADDER: ITS COMPLICATIONS, AND  
THE DIFFICULTIES AND DISADVANTAGES OF  
SECONDARY CHOLECYSTECTOMY.\*

BY DE WITT STETTEN, M.D.,

NEW YORK, N. Y.

WHILE the trend of surgical opinion, until quite recently, has been that cholecystectomy is the operation of choice in the vast majority of cases of gall-bladder disease, the question is as yet by no means definitely settled. It is quite generally agreed that the gall-bladder should not be extirpated in any form of irremovable occlusion of the common duct. Most surgeons believe that cholecystectomy is somewhat more of a procedure than cholecystostomy and that, therefore, the latter operation should be performed, as an emergency measure, in very critical cases, especially in very severe, acute, fulminating infections, in cases where there are very extensive adhesions or other great technical difficulties, in late pregnancy, in the very aged, in much debilitated, undernourished or very fat patients, in advanced cardiac decompensation or pulmonary tuberculosis, in serious chronic bronchitis or emphysema, in extreme anemia, in hemophilia, in uncontrollable diabetes, in renal insufficiency, or in the presence of marked or protracted cholemia. It is a universal opinion that a gall-bladder which is seriously damaged or ulcerated, which is the seat of malignant disease, or whose cystic duct is obliterated should be removed. In all the other cases, which really comprise the great bulk of

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gall-bladder operations, there is still considerable divergence of opinion, with the tendency just at present for the pendulum to swing backward toward retaining the gall-bladder unless that organ is hopelessly diseased. Much is now being written of the functions of the gall-bladder and its importance to the organism. The *Journal of the American Medical Association* of November 26, 1921, and February 25, 1922, discusses the subject editorially, as does, *Surgery, Gynecology and Obstetrics* in March, 1922. These editorials, which are based upon the most modern research on the subject, are frankly warnings to the surgeon not to consider the gall-bladder as a functionless organ. Other writers take quite the opposite view and regard the gall-bladder of almost as little importance to the organism as they do the appendix. One of the most recent contributions with this leaning is a very complete analysis of the subject, with full bibliography, by Harer, Hargis and Van Meter.<sup>7</sup> Their conclusions, aside from the belief that the gall-bladder acts as a concentrator of the bile by lymphatic absorption, almost agree with those of Woods Hutchinson<sup>8</sup> and others in considering the gall-bladder a vestigial structure. Two other very recent papers by Jacobson and Gydesen,<sup>22</sup> and by Auster and Crohn,<sup>23</sup> based upon experimental studies, have similar inclinations. The former see little use for the gall-bladder, except the minimizing of extremes of pressure in the biliary system, while the latter feel that the usual bile flow disregards the gall-bladder altogether, that the gall-bladder has no contractile function to speak of, that its outflow is in the nature of an overflow incontinence, but that, under pathological conditions, it may relieve intraductal pressure. Both papers refer to the concentration of the bile in the gall-bladder by dehydration, but both likewise indicate that its removal in the human being produces no definite, clinically demonstrable, deleterious effects.

Papers are still being published in which are discussed the indications and contraindications for cholecystectomy as against cholecystostomy. To be sure, the Mayo Clinic, whose dicta exert a marked influence on surgical thought in the United States, has come out strongly for cholecystectomy as the routine procedure—as demonstrated by the chapter on Gall-bladder Surgery in the latest volume of *Keen's Surgery* by William J. Mayo and Donald C. Balfour.<sup>17</sup> According to this article, there are no two sides to the question. This opinion from Rochester, however, is only a comparatively late development, having gradually come to the fore about nine years ago. As recently as 1908, William J. Mayo<sup>15</sup> expressed himself emphatically against the removal of the gall-bladder as the operation of choice, and only in 1914 did he,<sup>16</sup> by a very gradual and unostentatious transition, show that he was changing his mind. Since that time, the opinion of the Mayos, based upon their enormous material, has been quite consistently

in favor of cholecystectomy. Yet it was not before 1916, in a symposium upon "*Cholecystostomy versus Cholecystectomy*," at the Clinical Congress of Surgeons of North America, that Charles H. Mayo<sup>14</sup> made a statement, clear-cut and crystallized, favoring the latter operation. At that same symposium, Lund<sup>12</sup> was, if anything, more emphatic than Mayo, while Deaver<sup>2</sup> had much more to say in favor of cholecystostomy than either of the other two. The opinion of Lund and the Mayos, however, is by no means universally accepted even in this country. The latest editions of such standard text-books as Binnie<sup>1</sup> and Ochsner (*Ransohoffs*<sup>18</sup>) still discuss the *pros* and *contras* of the subject at length, and articles are constantly appearing in the surgical literature condemning routine cholecystectomy and advocating conservation of the gall-bladder. So far as the European surgeons are concerned, there still seems to be considerable doubt in their minds. Kehr,<sup>10, 11</sup> in his most recent publications, before his death, staunchly advocated cholecystectomy, but his opinion is by no means generally shared by the other surgeons of Europe, particularly by our English colleagues.

The usual method of argumentation in favor of cholecystostomy as against cholecystectomy has been to emphasize the fact that the gall-bladder is an important organ with vital functions which are more or less clearly understood. It is contended that its routine removal involves serious dangers or disadvantages to the individual, such as dilatation of the bile ducts, relaxation of the sphincter of Oddi and subsequent ascending infection of the biliary passages, or digestive disturbances from dribbling of bile, so-called "biliary incontinence," while its retention is of great value and importance in storing and concentrating the bile, and in regulating its tension in the biliary system and its intermittent flow into the duodenum by "contrary" or "reciprocal" innervation. I believe that it might be worth while now to approach again the question from the reverse point of view, to analyze specifically the complications that may arise from retaining the gall-bladder and to study in detail the difficulties and disadvantages of a secondary removal of that organ. I have tried to base my deductions mainly upon personal observations in a series of cholecystostomized patients, who, either soon after the drainage of the gall-bladder, developed troublesome symptoms, or whose recurrence may have been postponed for periods varying from a few months to many years. The majority of these cases have later come to secondary cholecystectomy.

I shall first discuss:

**I. The Complications of the Retained Gall-bladder.** Although some of the cases have not come to secondary removal of the gall-bladder, even these show rather well-defined clinical pictures, so that they can be readily classified with the operative cases.

On the basis of the essential lesions found at operation, I have attempted to group the cases in the following manner:

1. *FISTULÆ*. One of the most frequent complications of cholecystostomy is the formation of a persistent fistula. There are two distinct types of fistula—mucous and biliary—depending, as the names imply, upon whether the discharge is merely mucous secretion from the gall-bladder or a drainage of bile. Both types of fistulæ may be continuous. They are, however, usually intermittent in character, giving rise to pain in the gall-bladder region, frequently chills and fever, and, in the case of biliary fistulæ, distinct icterus, when they are closed. Immediate relief follows the spontaneous or artificial opening of the fistula and the discharge of the retained mucus or bile.

(a) *Mucous Fistulæ*. Mucous fistulæ following cholecystostomy are invariably due to occlusion of the cystic duct of the retained gall-bladder, the discharge being the secretion of its mucous membrane.

This occlusion may be due either to a complete inflammatory or cicatricial stricturing of the cystic duct, or to a retained calculus, impacted in the duct itself or in the neck of the gall-bladder, or to both. The mucous fistula may develop immediately after cholecystostomy or there may be a period of biliary drainage. Then, as the cystic duct becomes more or less occluded by stricture or by impaction of a calculus, only mucus is discharged. The stricture may open or the calculus may move and the fistula may then discharge bile for a time and close. If the stricture closes or the calculus becomes impacted again, the mucous fistula may reform before or after the external wound has closed. This intermittent mucous-biliary fistula is not an uncommon variety. Should conditions favor it (see under Biliary Fistulæ), after the cystic duct occlusion has been overcome, a mucous fistula may become converted into a persistent biliary fistula. Let me mention a few examples of mucous fistula:

CASE I.—(Office.) Female, aged eighty-four years. Twenty-three years ago she was operated upon for gall-stones. Numerous calculi were removed and the gall-bladder was drained. The wound has never closed. The discharge has always been mucous. Owing to the patient's advanced age, operation is, of course, not to be considered. The cystic duct must be occluded—probably obliterated by cicatrization (Fig. 1).

CASE II.—(Office.) Female, aged thirty-three years. In 1916, she had been operated upon for gall-stones with drainage of the gall-bladder. Bile drained for a short time and then a mucous fistula developed which refused to close permanently. When the secretion ceased, the patient ran high temperatures, and suffered

from severe pain in her gall-bladder region. I advised cholecystectomy, which was done in her home city a year after her first operation. A strictured cystic duct was found (Fig. 1). The patient has been perfectly well since.

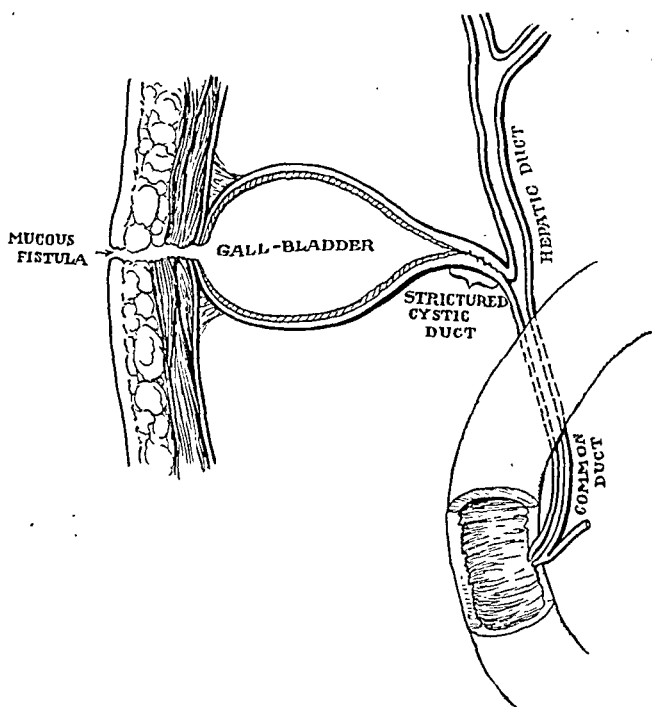


FIG. 1.—Cases I and II. Mucous fistula, due to total stricture of cystic duct.

CASE III.—(No. P. 1334, 1919.) Male, aged fifty-two years. On March 18, 1918, he was operated upon for an acute empyema of the gall-bladder. No stones were recovered and the gall-bladder was drained. The wound did not close. There was an alternating mucous and biliary fistula: I performed a cholecystectomy on March 28, 1919, twelve months after his first operation, and removed a shrunken and thickened gall-bladder, very adherent to the anterior abdominal wall with a calculus in the cystic duct, not absolutely impacted, but quite snug (Fig. 2). Prompt healing followed.

CASE IV.—(Nos. P. 2385, 1920, and 3030, 1920.) Female, aged sixty-four years. I first saw her in April, 1918, after she had been operated upon for an acute empyema of the gall-bladder some months previously. In addition to a large ventral hernia through the wound there was a mucous, and at times a mucous-biliary fistula. This fistula occasionally closed and when it did there was a rise of temperature and pain in the gall-bladder region. Owing to the patient's poor general condition, I advised temporizing and

the fistula finally seemed to heal without untoward symptoms. On August 18, 1920, she developed an acute intestinal obstruction, due to a band in the gall-bladder region tying off a loop of ileum. I released the band, separated numerous intestinal adhesions and repaired the hernia. She made a satisfactory recovery and remained well until November 22, 1920, when she developed an acute abscess in the old gall-bladder which broke through into the abdominal wall. The pus was slightly bile-stained. A cholecystectomy revealed a contracted gall-bladder with a calculus in the cystic duct, rather tightly impacted (Fig. 2). To the gall-bladder, and under the surface of the liver, the duodenum and hepatic flexure of the colon were densely adherent (Fig. 18).

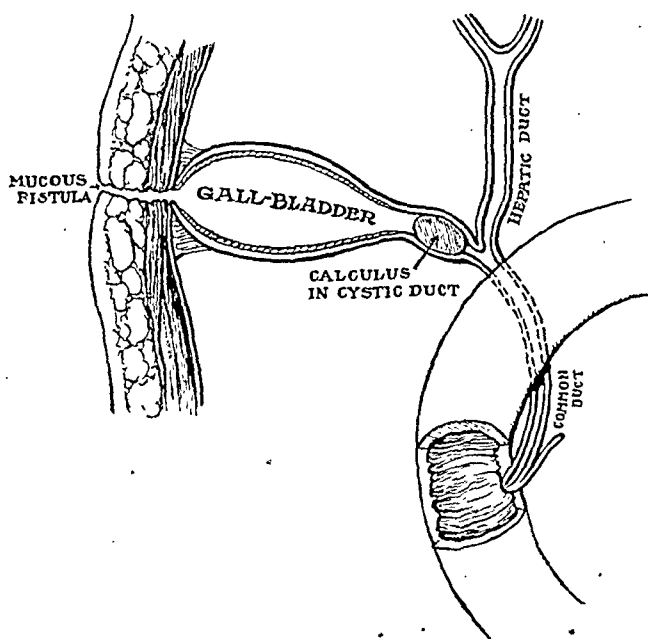


FIG. 2.—Cases III and IV. Mucous fistula, due to impacted calculus in cystic duct. Shrunken gall-bladder.

In the two previous cases, of course, the calculus in the cystic duct was overlooked at the first operation. Had a cholecystectomy been done this oversight would not have occurred. The cystic duct stone would have been removed with the gall-bladder.

The following case illustrates how the retention of an impacted calculus in the neck of the gall-bladder, combined with a total stricture of the cystic duct, served to produce a mucous fistula, which would have been avoided by primary cholecystectomy:

CASE V.—(No. P. 3150, 1922.) Female, aged thirty-one years. This was a patient of Dr. Hermann Fischer's, who, four months previously had been operated upon for some acute gall-bladder

disease accompanied with high fever and slight jaundice. The gall-bladder was drained and the patient does not know whether or not any stones were removed. The fistula never healed. At first it drained pure bile, but later only a slightly yellowish-colored mucus. She also complained of pain in the region of the fistula and fullness and soreness in the epigastrium after eating. She was operated upon, November 20, 1923, by Dr. Fischer, who excised the fistula and with much difficulty and hemorrhage, isolated and removed the gall-bladder which was imbedded in a mass of adhesions including the liver, stomach, duodenum and hepatic

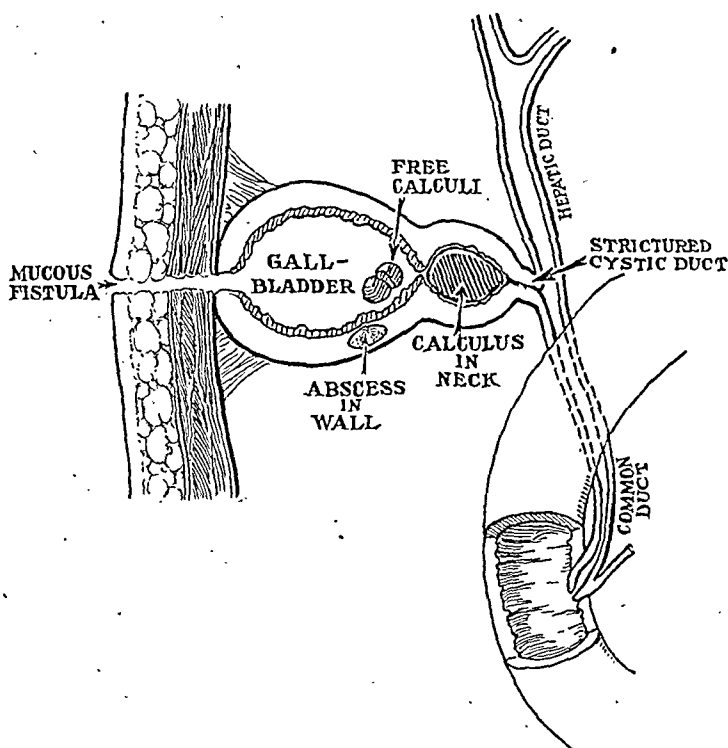


FIG. 3.—Case V. Mucous fistula, due to both impacted calculus in neck of gall-bladder and to total stricture of cystic duct. Thickened gall-bladder with two additional free calculi in lumen and small chronic abscess in wall.

flexure of the colon. The gall-bladder was a thickened, somewhat contracted organ. In the main cavity were two small calculi and lodged in the neck, which was separated from the main cavity by an hour-glass contracture, was a large ovoid calculus. The cystic duct was completely strictured and in the wall of the gall-bladder was a small chronic abscess (Fig. 3). The convalescence was uneventful.

(b) *Biliary Fistulae*. Biliary fistulae are due to a variety of causes. In some instances the biliary fistula is not due to the retained gall-bladder, *per se*, but to an incomplete operation and

the leaving of calculi in the common duct. In a measure, the neglect to dissect out the gall-bladder and expose the ducts to proper inspection and palpation is responsible for even this complication. Let me illustrate:

CASE VI.—(No. 1716, 1912.) Male, aged thirty-seven years. In February, 1912, he was operated upon for gall-stones. Several fair-sized calculi were removed from the gall-bladder and the gall-bladder was drained. A continuous biliary fistula developed and reoperation by me on April 15, 1912, about two months after his first operation, disclosed the fact that a large stone in the common duct, impacted at the papilla, had been overlooked.

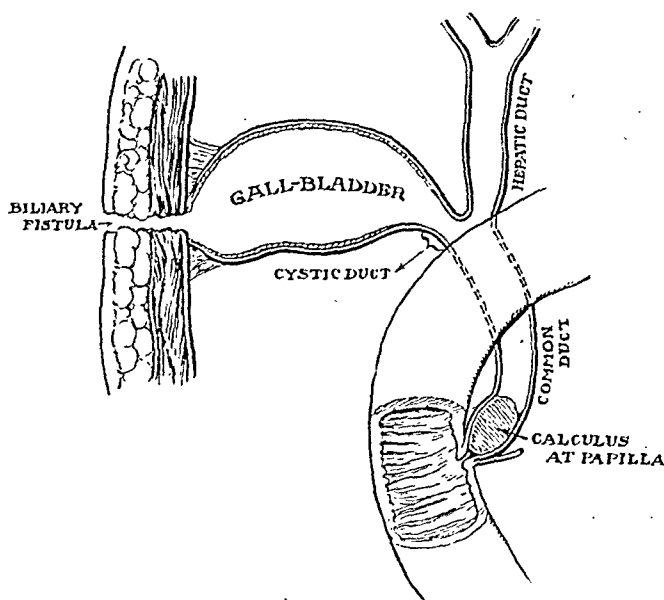


FIG. 4.—Case VI. Biliary fistula, due to impacted calculus in common duct at papilla. Hepatic and common ducts somewhat dilated.

The thickened gall-bladder was imbedded in adhesions, and the hepatic and common ducts were somewhat dilated. He was cured by choledochotomy, extraction of the calculus, cholecystectomy and hepatic drainage (Fig. 4). Microscopical examination of the gall-bladder showed a chronic cholecystitis.

CASE VII.—(No. 862, 1917.) Female, aged sixty-one years. In 1915, she had been operated upon for gall-stones with jaundice. One large, solitary calculus was removed from the gall-bladder and drainage instituted. When the drainage of bile ceased, she developed very severe pain in the gall-bladder region and one year after her first operation a cholecystectomy was performed by another surgeon. She then developed a biliary fistula, which was

almost continuous, except for an occasional stop. During the stoppage there was pain and fever. On February 12, 1917, eight months after her second operation, I excised the fistulous tract, removed two moderately large stones from the dilated common duct and drained the biliary system (Fig. 5). The fistula closed promptly.

A second very common form of biliary fistula after cholecystostomy is that due to the formation of a so-called "lip" or mucocutaneous fistula, where the mucous membrane of the gall-bladder, adherent to the abdominal wall, becomes continuous with the epithelium of the skin. This cannot heal any more than a fecal fistula of the same character. Typical cases of this nature are the following:

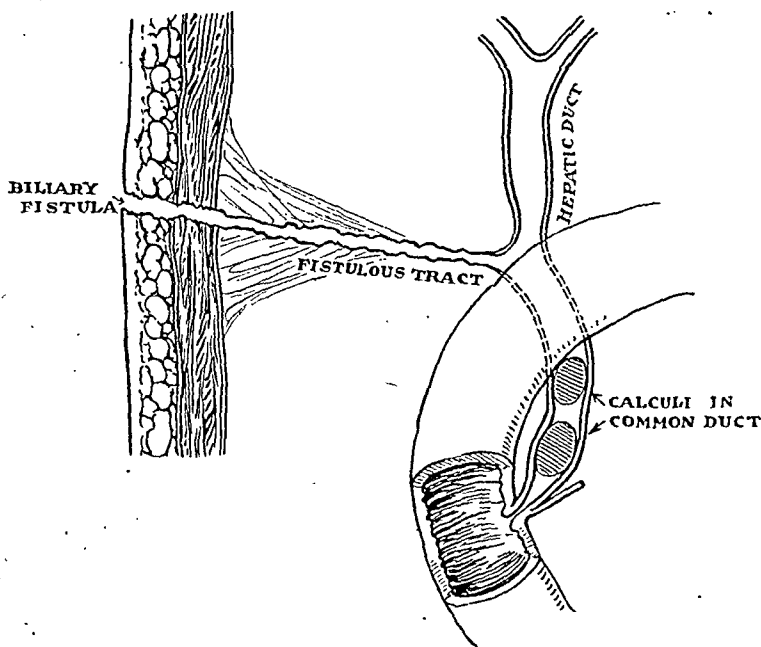


FIG. 5.—Case VII. Biliary fistula after secondary cholecystectomy, due to retained calculi in dilated common duct.

CASE VIII.—(Private.) Male, aged thirty-six years. On August 3, 1905, a cholecystostomy was done for a severe, septic empyema of the gall-bladder, and a very large calculus, practically the cast of the gall-bladder, was extracted. I assisted Dr. Frederic Kammerer at this operation and later had the after-care of the patient. A total biliary fistula developed, due to the growth of the mucous membrane to the skin (Fig. 6). The "cork experiment" showed that the common duct was patent, and following the teachings of a time when cholecystectomy was not as popular as it is today, on October 26, 1905, nearly three months after the primary operation, Dr. Kammerer successfully closed the fistula by loosening the mucous membrane from the skin and



suturing the gall-bladder, much as we close a fecal fistula at the present time.

CASE IX.—(No. 2892, 1913.) Male, aged forty years. Two months previously the gall-bladder had been drained and several calculi removed. The biliary fistula refused to close on account of the proximity of the mucous membrane of the gall-bladder to the skin (Fig. 6). Some bile flowed into the intestine. On June 18, 1913, I separated the fistulous opening from the abdominal wall and succeeded in closing it by purse-string inverting sutures. Today I would unhesitatingly perform a cholecystectomy in a similar case.

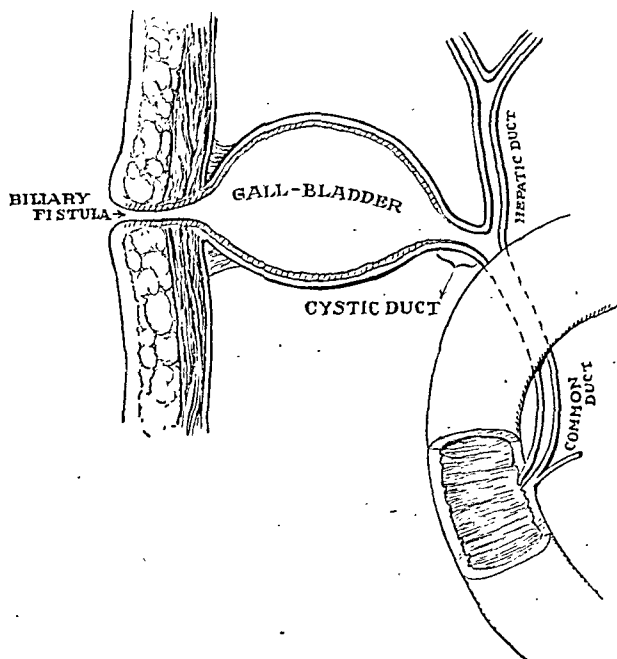


FIG. 6.—Cases VIII and IX. Biliary fistula, due to formation of mucocutaneous fistula.

A third variety of biliary fistula is due to a kinking or angulation of the junction of the hepatic and common ducts, because of the pull of the gall-bladder which is attached to the abdominal wall, and which, after drainage, frequently shrinks decidedly. I published such a case in 1913.<sup>19</sup>

CASE X.—(No. 3693, 1912.) Female, aged nineteen years. I performed a cholecystostomy on July 24, 1912, and removed five medium-sized stones. Drainage was carried out in the usual manner. Bile drained freely at first, but then ceased. Severe pain and icterus developed, and the gall-bladder wound was reopened, with resulting profuse biliary drainage. This drainage

of bile continued for nearly a month, and on August 17, 1912, I reoperated. I found a much changed and contracted gall-bladder, adherent to the anterior abdominal wall, with a kink at the junction of the hepatic and common ducts, evidently due to the pull of the gall-bladder (Fig. 7). The angulation at the junction of these ducts was less than 45 degrees, and an actual valve-like formation prevented the bile flowing from the liver in its normal direction. There were no further calculi in the gall-bladder or ducts. The hepatic duct was markedly dilated, and the common duct narrowed, but when the gall-bladder was loosened and removed, and the common duct opened, a large probe was easily inserted into

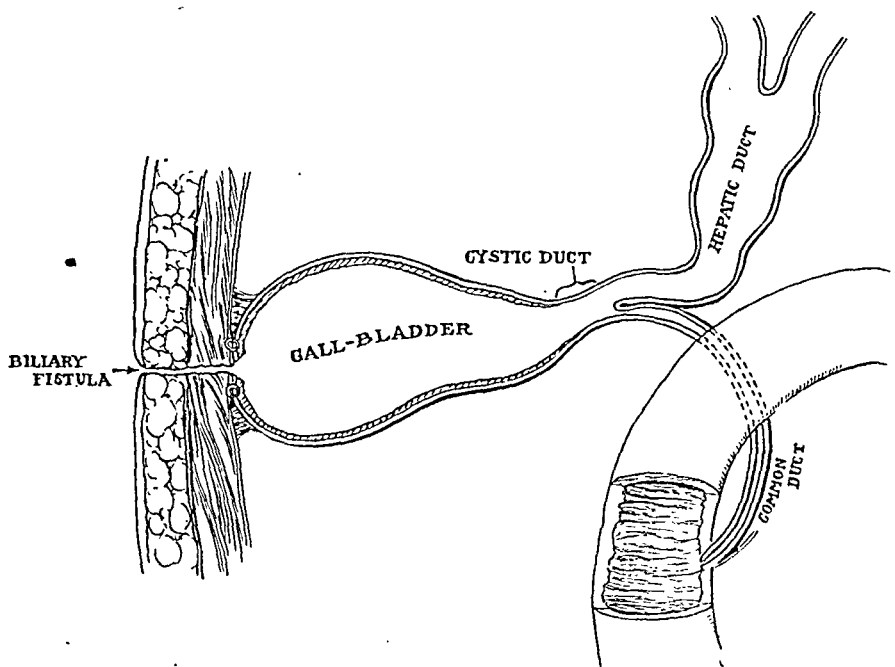


FIG. 7.—Case X. Biliary fistula, due to angulation of junction of hepatic and common ducts. Marked dilatation of hepatic duct, narrowing of common duct and valve-like formation at junction.

the duodenum through the papilla. The fistula closed promptly after cholecystectomy and the resultant straightening of the hepatic and common ducts.

Another case that might be mentioned in this group, although there was no actual fistula but rather the symptoms of common duct obstruction due to a marked contraction of the gall-bladder after cholecystostomy, is the following:

CASE XI.—(No. 2739, 1908.) Female, aged thirty-three years. She had been operated upon three weeks previously, July 20, 1908,

by another surgeon. Stones had been removed and a cholecystostomy performed. The bile drainage ceased promptly and the wound began to close when the patient became jaundiced and severe, cramp-like pains in the gall-bladder region developed. It was assumed that a stone in the common duct had been overlooked, and on August 10, 1908, I attempted to reopen the gall-bladder to establish drainage. With great care I tried to expose the gall-bladder and what seemed to be that organ, firmly adherent to the anterior abdominal wall, was finally exposed and opened. Bile escaped and a tube was inserted for drainage. The drained organ proved to be the duodenum (Fig. 17), and a duodenal fistula developed which unfortunately resulted in the death of the patient from inanition, in spite of all efforts at closure, including gastroenterostomy and pyloric exclusion. Postmortem examination

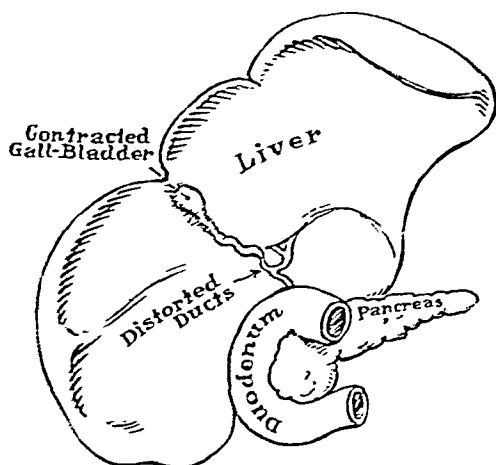


FIG. 8.—Case XI. Shrunken gall-bladder with distortion of ducts.

revealed an extremely shrunken gall-bladder continuous with the old sinus tract and some distortion of the ducts due to the pull of the shrunken organ (Fig. 8). There were no calculi in the gall-bladder or ducts and the ducts were patent.

It should here be noted that, in certain instances, a cholecystostomy wound will close more or less permanently, even if the cystic or common duct is obstructed by stricture, distortion or the retention of a calculus, provided the obstruction is only partial at the time. If, however, the occlusion becomes more complete or infection supervenes, the clinical picture of hydrops or empyema of the gall-bladder, common duct obstruction or cholangitis will, of course, develop just as in cases that have not been previously operated upon.

2. RETENTION OR REFORMATION OF CALCULI WITH ATTENDANT LESIONS. In addition to those cases cited under the previous

heading, in which calculi in the cystic or common duct had been overlooked, in a measure because primary cholecystectomy was not done, and where a mucous or biliary fistula formed, there are other cases of cholecystostomy in which calculi are inadvertently left free in the gall-bladder. In these latter cases the operative wound closes, but symptoms of biliary colic recur, with or without signs of acute infection or jaundice, often very promptly after operation, as, for example:

CASE XII.—(No. P. 1266, 1915.) Female, aged fifty-six years. Twenty-two years ago she was operated upon for gall-stones. A number of stones were removed and the gall-bladder was drained. Four and a half weeks after the operation she had a typical attack of biliary colic and claims that calculi were found in the stool. Since then she has had more than a dozen attacks of rather severe, gall-stone colic, followed, usually, by jaundice. For the past few years the attacks have been somewhat less frequent and less severe and she prefers to postpone radical measures.

In other cases it is probable that calculi have reformed in the retained gall-bladder. Of course, it is well-known that gall-stones may form in the common and hepatic ducts and even in the liver, but the chance of reformation is greatly increased by the retention of the gall-bladder, because this organ is the principal seat of the process. To be sure, one can never be certain that the so-called cases of recurrence are really instances of recurrence at all. They may be the result of incomplete operation and non-removal of all the stones present at the time of the original operation, as in the case just described. I have, however, met with certain cases that seem to be *bona fide* recurrences. With the recurrence of the calculi, any sequel may develop, as with the primary stones, as, for instance, in the cases mentioned below, namely empyema of the gall-bladder, common duct obstruction, or chronic cholecystitis with lodging of the calculus in the cystic duct.

CASE XIII.—(No. 307, 1921.) Male, aged forty years. Eight years ago he had been operated upon for gall-stones. Several stones had been removed and a cholecystostomy had been done. The drainage sinus closed within a normal period, and the patient remained well for about three years. He then had repeated attacks referable to the gall-bladder, finally culminating in a very acute condition. On January 18, 1921, I operated upon him for an acute empyema of the gall-bladder. I found and removed a very large, very thick-walled and inflamed gall-bladder adherent to the anterior abdominal wall and distended with seropus. The mucosa was gangrenous. Free in the gall-bladder were two calculi, the size of hazel-nuts (Fig. 9). The cystic duct was completely stenosed. The patient made an uneventful recovery. The original operation had been performed by a very competent surgeon, and it is incon-

ceivable that these two large stones could have been overlooked if they had been in the gall-bladder at the time, nor could they have been left in the ducts and later have entered the gall-bladder, because the wound healed promptly after the first operation.

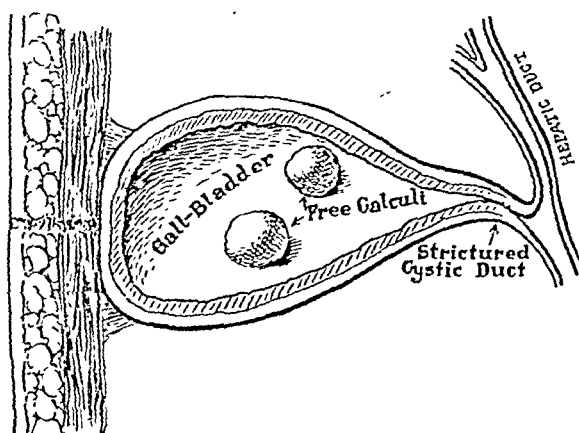


FIG. 9.—Case XIII. Thickened and distended gall-bladder with recurrent calculi. Total stricture of cystic duct.

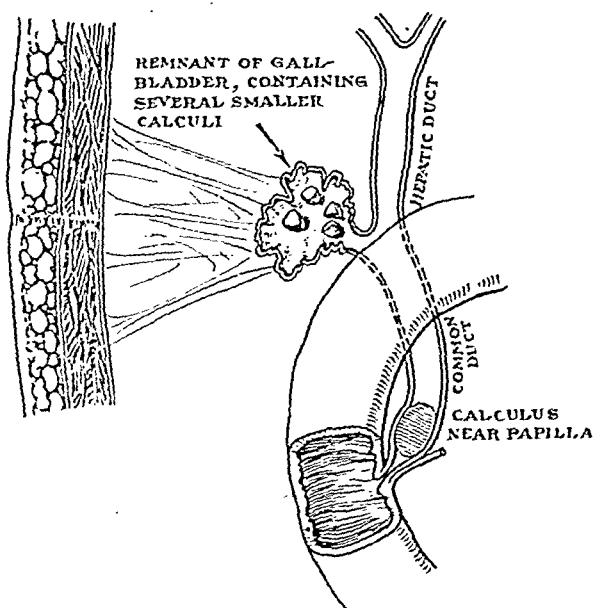


FIG. 10.—Case XIV. Recurrent calculi in remnant of gall-bladder and dilated common duct.

CASE XIV.—(No. P. 3282, 1920.) Female, aged sixty-seven years. In 1912, she had been operated upon for gangrene of the gall-bladder. A large number of gall-stones had been removed

and likewise a portion of the gall-bladder. At the time of the operation there was no evidence of calculi in the ducts. She was well until a little over a year ago when she developed symptoms that pointed to an intermittent common duct obstruction. She had had three or four attacks of pain resembling biliary colic, followed by jaundice. At operation, December 18, 1920, I found the remnant of the gall-bladder imbedded in adhesions. The gall-bladder stump contained several smaller stones, and in the dilated common duct was a large stone near the papilla (Fig. 10). She was cured by choledochotomy, extraction of the common duct stone, the removal of the remains of the gall-bladder and its contents and hepatic drainage. In this case it is possible that the presence of the calculi was the result of an incomplete operation, although the operating surgeon claimed that there was no recognizable evidence, at the time, of any remaining stones either in the gall-bladder remnant or in the ducts. Further, if these stones had not reformed since the operation, it is almost inconceivable why the patient should have remained well for over seven years.

CASE XV.—(No. P. 403, 1922.) Female, aged forty-one years. A large solitary gall-stone was removed and the gall-bladder drained in 1916. For four years she was in moderately good health, but two years ago she began to suffer from pain, sometimes diffused, sometimes localized in the right hypochondrium where there was definite sensitiveness to the touch. There was a diarrheal tendency. Operation on February 22, 1922, disclosed an infiltrated, friable gall-bladder, imbedded in omental adhesions and adherent to the duodenum. In the cystic duct was a typical solitary, non-facetted, cholesterin calculus, the size and shape of an olive (Fig. 11). The patient was entirely freed of her symptoms by cholecystectomy. The gall-bladder showed the usual changes of a chronic cholecystitis.

In this case the character of the stone is almost conclusive evidence of its being a definite example of reformation. The relative freedom from symptoms for four years after the first operation and the recurrence of her illness two years ago corroborates this inference.

3. ADHESIONS. There is a group of cases after cholecystostomy where the patients are not cured and where the symptoms seem to be due essentially to adhesions between the abdominal wall and the retained gall-bladder. When one realizes that adhesions, merely of the omentum to the anterior abdominal wall, following an appendectomy or a gynecological laparotomy, are often the source of such disturbances that relaparotomy becomes necessary to loosen these adhesions, as I have observed in quite a series of

cases, it is understandable that a gall-bladder, with the adjacent liver edge, that becomes tightly plastered to the abdominal scar can cause sufficiently annoying symptoms, either directly or reflexly, to make its victim a real invalid. Frequently, these adhesions also include the duodenum and pyloric portion of the stomach and, often, even the hepatic flexure of the colon. The following are my observations where I believe the adhesions, *per se*, were, in the main, responsible for the continued illness of the patient:

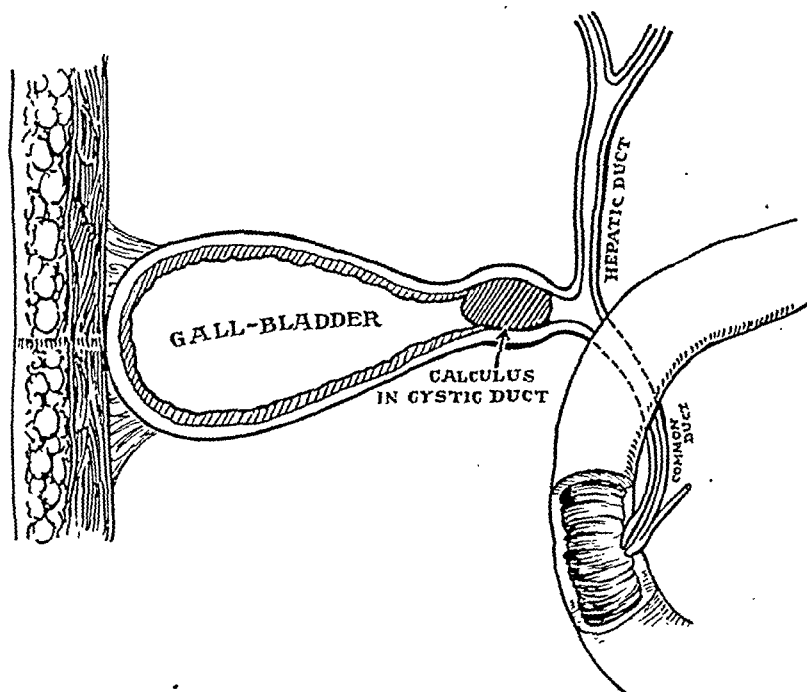


FIG. 11.—Case XV. Large solitary recurrent calculus impacted in cystic duct. Somewhat thickened gall-bladder adherent to anterior abdominal wall.

CASE XVI.—(U. S. Army Embarkation Hospital No. 4.) Female, aged thirty-six years. In 1916, she had been cholecystostomized for multiple calculi. She was never well after the operation, but suffered continuously from annoying pains in the gall-bladder region, particularly on standing and bodily exertion. As she was a nurse, this handicapped her considerably and, finally, in April, 1919, three years after her first operation, I did a cholecystectomy. I found a rather elongated gall-bladder, very densely adherent to the anterior abdominal wall, in such a way that the edge of the liver was actually turned back upon itself. Adhesions between the liver edge and the anterior abdominal wall were also present (Fig. 12). After the loosening of all adhesions and the removal of the gall-bladder, the patient was entirely freed of her symptoms.

CASE XVII.—(No. 3475, 1921.) Female, aged thirty-nine years. About five years ago the gall-bladder had been drained for a cholecystitis without stones. There was more or less continuous pain in the gall-bladder region following the operation. On June 20, 1921, I operated upon this patient and found the gall-bladder imbedded in omental adhesions and adherent to the anterior abdominal wall at the costal border. The adhesions were separated and the gall-bladder removed. Microscopical examination of the gall-bladder showed a chronic cholecystitis. Her pain ceased after the operation.

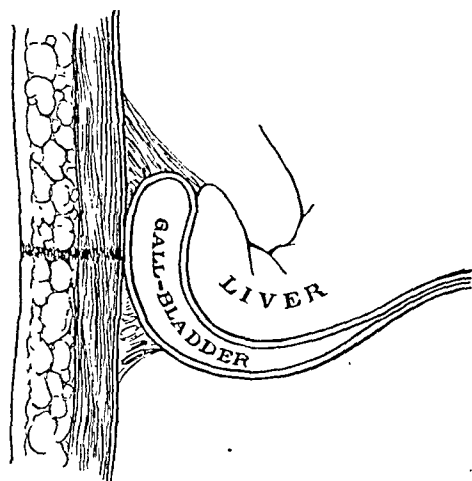


FIG. 12.—Case XVI. Elongated gall-bladder densely adherent to anterior abdominal wall and turning liver edge back upon itself.

CASE XVIII.—(No. 3229, 1921.) Male, aged twenty-two years. Two and a half years ago he had been operated upon for some gall-bladder trouble. The gall-badder had been drained, although no stones were found. The patient remained quite well for a year and nine months, when he began to vomit after every meal and suffered from cramp-like abdominal pains. The bowels moved freely, even with a diarrheal tendency. This vomiting continued for three months, and became so severe at the end of that time that the patient came to the hospital in an extremely weakened condition. He was so ill that rectal feeding was necessary. The roentgen-ray examination was not conclusive, but suggested adhesions of the pylorus and duodenum to the gall-badder region. An exploratory laparotomy by me on June 1, 1921, revealed a gall-bladder adherent to the anterior abdominal wall and imbedded in dense adhesions, and adhesions of the pylorus and duodenum to the gall-bladder. The adhesions were separated, the gall-bladder removed and the patient made an uneventful recovery.



CASE XIX.—(No. 1652, 1922.) Male, aged thirty-eight years. In 1919, his gall-bladder was drained for what was supposed to be a cholecystitis without stones. For some years, he has been a sufferer from marked gastric symptoms which the roentgen-ray showed to be due to a deep, penetrating ulcer of the lesser curvature. On March 22, 1922, I performed a partial gastric resection with gastroenterostomy. The operation was much complicated and protracted by the adhesions between the gall-bladder, anterior abdominal wall, omentum and duodenum. The isolation of the duodenum was accomplished only with the greatest of difficulty. His stomach symptoms have been relieved, but he still has pain in the gall-bladder region and a secondary cholecystectomy is now being considered.

4. RECURRENT CHOLECYSTITIS. The cases in this group merge more or less with those in the group discussed just previously. In Case XVII, for instance, the gall-bladder was much thickened and microscopical examination showed a chronic cholecystitis. It is possible that some of the symptoms were due to this chronic inflammatory condition. It is difficult to separate the cases in which the symptoms are due purely to adhesions, and those in which the symptoms are due to a recurrence of an inflammatory lesion in the gall-bladder. In most cases, both lesions are probably responsible for lack of cure. The cholecystitis may be either in the form of recurring acute or subacute attacks or may be more of a chronic affair. The following are illustrations of where the cholecystitis, apparently, was the predominating factor in the illness of the patient:

CASE XX.—(No. P. 2286, 1908.) Female, aged thirty-five years. On June 17, 1908, I performed a typical cholecystostomy for a severe, acute empyema of the gall-bladder, which contained numerous small stones. The wound healed very slowly—a fistula, first biliary, then mucous, remaining for months. About one year later she had a typical attack of acute cholecystitis, with a temperature of 104° F., slight icterus and an exquisitely sensitive gall-bladder region. This attack subsided and the patient remained fairly well for over ten years. In 1920, she had a number of moderately severe attacks, which were clearly referable to the gall-bladder, and I advised a secondary cholecystectomy. She has not yet consented to have this done, and manages to get along fairly well between attacks.

CASE XXI.—(No. P. 2862, 1921.) Male, aged sixty-seven years. In 1901, he had a cholecystostomy performed. Numerous stones were removed from the gall-bladder and the patient made a satisfactory recovery. In the past three or four years this patient

has had several attacks of decided discomfort in the gall-bladder region. There is some sensitiveness to pressure and coincident digestive disturbance, referable particularly to the intestines. During the attack there is diarrhea and flatulence, presumably due to an enterocolitis, secondary to an exacerbation of infectious processes in the gall-bladder.

CASE XXII.—(Office.) Female, aged twenty-seven years. Two years ago several gall-stones were removed and cholecystostomy performed. She has recently consulted me, complaining of constant indigestion and pain in the right upper abdomen. The gall-bladder region is sensitive to pressure. Cholecystectomy for recurrent cholecystitis with adhesions has been advised.

CASE XXIII.—(Office.) Female, aged sixty-two years. Very recently I was consulted by this patient, who had been operated upon fifteen years ago. A very large gall-bladder containing over a hundred calculi was found. The stones were removed and the gall-bladder drained. She has never been well since the operation. She suffers from continuous pain in the right hypochondrium. At times this pain increases in severity and then she has attacks of nausea and vomiting. During these attacks there is a moderate rise of temperature. The gall-bladder region is markedly sensitive to pressure. Her trouble is undoubtedly due to a recurrent cholecystitis associated with adhesions between the gall-bladder and anterior abdominal wall. I have advised her to have her gall-bladder removed, and I believe that, sooner or later, she will be forced to follow my advice.

CASE XXIV.—(Office.) Female, aged twenty-four years. A little over a year ago she was operated upon for numerous very fine biliary calculi, which were removed, and the gall-bladder was drained. Five months after operation she had a very severe attack of pain in the gall-bladder region, probably due to a subacute cholecystitis. Since that time she suffers more or less continually with pain in her back and right hypochondrium, in all likelihood, the result of adhesions and chronic cholecystitis. Her appetite and digestion are poor. She is very sensitive to pressure in the gall-bladder region. I have advised cholecystectomy, and she is considering having the operation performed in the near future.

CASE XXV.—(Office.) Female, aged forty-three years. After an illness of five years, she was operated upon six years ago. A cholecystostomy was done and many small stones were removed. Recently, she has had attacks of discomfort in the gall-bladder region, with indigestion. There is distinct sensitiveness to pressure in the right hypochondrium. A diagnosis of recurrent chole-

cystitis with adhesions has been made and cholecystectomy has been advised.

CASE XXVI.—(Nos. P. 3339, 1913, and P. 790, 1921.) Female, aged thirty-eight years. On July 1, 1913, because of symptoms very definitely suggesting gall-stones, I operated and found a gall-bladder rather normal in appearance and loosely adherent to the duodenum. There were no calculi to be felt either in the gall-bladder or ducts. Adhesions were loosened and the gall-bladder retained. On March 21, 1921, because of persistent attacks of colicky pain in the gall-bladder region, I reoperated. Dense adhesions were found between the omentum, anterior abdominal wall, liver and gall-bladder and between the duodenum and gall-bladder. These adhesions were loosened and a rather thickened gall-bladder was found. Cholecystectomy was done. The cystic

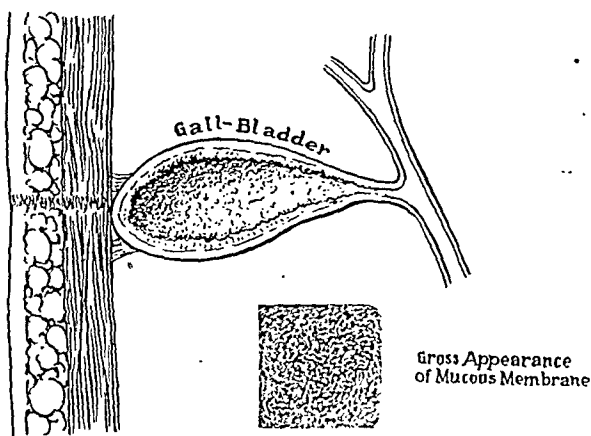


FIG. 13.—Case XXVI. Chronic cholecystitis. Insert shows gross appearance of papillary condition of mucous membrane.

duct was very friable and was ligated with difficulty. The gall-bladder showed a thickened wall with a mucosa studded with papillary excrescences (Fig. 13). Microscopical examination showed that the changes in the gall-bladder were purely of a chronic inflammatory nature. Of course, in this case the gall-bladder had not been drained. It was, however, an example of that condition, now so well recognized, namely, chronic cholecystitis without stones, where the gall-bladder should have been removed in the first instance. It is included in this paper because it is my conviction that even if the gall-bladder had been drained at the first operation, a secondary cholecystectomy would have been necessary. The patient has had no attacks since the removal of her gall-bladder.

A case somewhat similar to the preceding, but which has not yet come to reoperation, follows:

CASE XXVII.—(No. P. 3432, 1922.) Female, aged thirty-four years. Since 1903, after an attack of typhoid fever, patient has suffered from severe attacks of pain in the right upper abdomen with vomiting. She was not relieved by an appendectomy in 1910, and six months later the gall-bladder was examined but, as no calculi were found, it was not removed and merely some adhesions were loosened. In 1914, an ileocolostomy was done because of very dense adhesions at and kinking of the hepatic flexure of the colon. Her symptoms were not relieved, and she is now a chronic invalid. Upon examination, there is definite sensitiveness in the right hypochondrium. While it is possible that some of her trouble is due to adhesions and the presence of the unilaterally excluded loop of cecum, ascending and part of the transverse colon, there is little doubt that much of her trouble is the result of recurrent attacks of cholecystitis and secondary adhesions. A cholecystectomy with possibly a resection of the excluded loop of colon, in one or two stages, has been advised and is now under consideration by the patient.

The following is an example of recurrent cholecystitis in the retained gall-bladder, culminating in a true empyema:

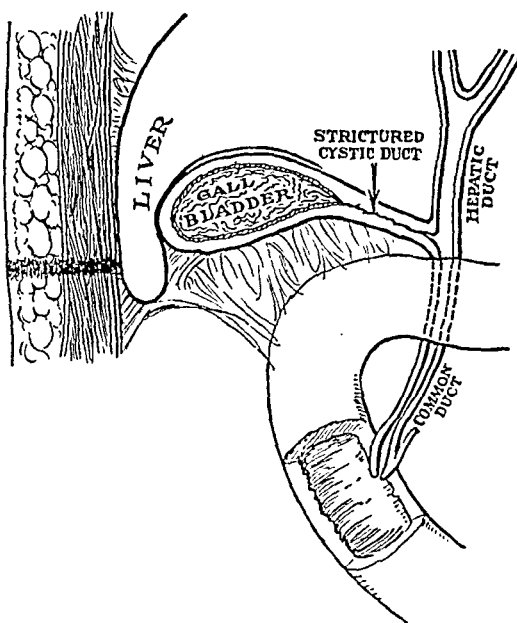


FIG. 14.—Case XXVIII. Shrunk gall-bladder filled with thick pus, with total stricture of cystic duct. Gall-bladder imbedded in adhesions, with adhesions of liver to anterior abdominal wall and of duodenum to liver and gall-bladder.

CASE XXVIII.—(No. P. 8684, 1922.) Male, aged fifty years. Six years ago he had been operated upon for gall-stones, but the gall-bladder had not been removed. During the past six months, the patient has had three other severe attacks of pain in the right

upper abdomen, radiating to the back. He was seen by me suffering from what appeared to be an acute inflammation in the gall-bladder region, with a temperature of 103° F., complicated by a postoperative ventral hernia. Operation, on December 15, 1922, disclosed a thickened, shrunken gall-bladder, deeply imbedded in the liver and surrounded by a mass of adhesions of omentum, pylorus, duodenum, hepatic flexure of the colon and liver to each other and to the anterior abdominal wall. Cholecystectomy was performed with considerable difficulty, and hemorrhage, after the separation of the adhesions, and the hernia was repaired. The gall-bladder was a much diseased organ, and was filled with thick, yellowish pus, containing some calculous gravel. The cystic duct was obliterated, and the mucous membrane of the gall-bladder was largely destroyed (Fig. 14). Microscopical examination showed an acute suppurative inflammation with a necrosis of the mucosa and submucosa extending in places into the muscularis. An uneventful convalescence ensued. It is a curious coincidence that this patient is the brother of Case XIII, operated upon by me nearly two years previously, with almost an identical clinical history and surgical findings.

The next case strongly suggests a similar condition as in the one previously described, although it has not yet been reoperated upon:

CASE XXIX.—(No. 2571, 1923.) Female, aged seventy-six years. On April 6, 1911, she was operated upon for an empyema of the gall-bladder. Two large calculi were removed and the gall-bladder was drained. A biliary fistula persisted for about four months but finally healed. In 1913, an abscess in the old scar was reopened and again bile drained for ten weeks. Since then she has had occasional mild attacks of pain and discomfort in the right hypochondrium. On April 2, 1923, she had an attack of severe pain in the epigastrium, radiating to the right shoulder, with vomiting, temperature of 103° F. and followed by slight jaundice. There is some sensitiveness over the old scar in the gall-bladder region. The roentgen-ray examination shows an unusually marked dilatation of the duodenum, probably indicative of a chronic duodenal obstruction due to adhesions. The attack is subsiding, but it was obviously an acute cholecystitis with either retained or reformed calculi in the gall-bladder or cystic duct. On account of the patient's age, the advisability of reoperation is still under consideration.

Let me here say a word upon the subject of typhoid infections of the gall-bladder. As is well known, it has been quite definitely shown that the gall-bladder is the chief breeding place of the typhoid bacillus in typhoid carriers. Hence, even more so than in the ordinary catarrhal or suppurative inflammations of this organ, in acute, subacute or chronic typhoid cholecystitis or in

simple typhoid carriers without decided inflammatory changes, cholecystostomy is an entirely insufficient operation. Cholecystectomy is imperative and should be supplemented by hepatic drainage until a sterile culture is obtained as Garbat,<sup>6</sup> in his excellent monograph on the subject, has demonstrated. This is necessary not only for the sake of the patient, but also in the interests of the community.

Here, too, might be emphasized the possible danger to the individual of the chronically inflamed gall-bladder from an entirely different angle. I refer to the question of focal infection and its consequences. If diseased teeth or chronic tonsillar infection can produce arthritis, anemia, bronchial asthma or some other general constitutional disturbance it is quite rational to assume that a chronic cholecystitis may play a similar injurious role.

5. POSTOPERATIVE VENTRAL HERNIA AND HERNIA OF THE GALL-BLADDER. Obviously, the chances of a ventral hernia developing through the scar are greater when the gall-bladder has been drained than when it has been removed, and the wound closed more or less tightly (Cases IV and XXVIII). An occasional sequel of cholecystostomy is a ventral hernia, in which the gall-bladder becomes the contents of the hernial protrusion. The discomfort of the hernia is increased by the presence in the sac of this organ. The symptoms are much the same as those discussed in Group 3 under Adhesions, only possibly even more severe. Two cases of this nature follow:

CASE XXX.—(No. 61, 1916.) Female, aged twenty-five years. She had been operated upon in 1915 for gall-stones. Several stones had been removed and the gall-bladder drained. Eight months after this operation she had an acute attack of pain in the region of the wound with cramps and vomiting after meals. The symptoms continued intermittently for four months, when she was admitted to my service and a large ventral hernia through the old scar was found. On January 6, 1916, she was operated upon by Dr. Carl Eggers for a repair of the hernia, who found in the hernial sac an adherent and somewhat distended gall-bladder (Fig. 15). A cholecystectomy and hernial plastic were done. Microscopical examination in this case also showed a chronic interstitial cholecystitis. The patient remained quite well until very recently, when she had an attack of pain in the same locality. This pain may have been due to adhesions, but in all probability was more of a neurosis because it subsided after a brief course of palliative therapy.

CASE XXXI.—(No. 5766, 1921.) Female, aged forty-two years. In January, 1921, the gall-bladder was drained but no stones were

found. An enormous hernia developed through the scar. The patient was totally incapacitated by the pain and discomfort in this region. On September 29, 1921, I repaired the hernia by a plastic operation, but decided not to disturb the gall-bladder, which was imbedded in adhesions in the hernial sac. I felt that a cholecystectomy at this time might jeopardize the primary union of the hernial repair. The plastic healed solidly and the patient was greatly relieved for a time. Recently, she has again been troubled with symptoms seemingly referable to her gall-bladder and a cholecystectomy is now under advisement.

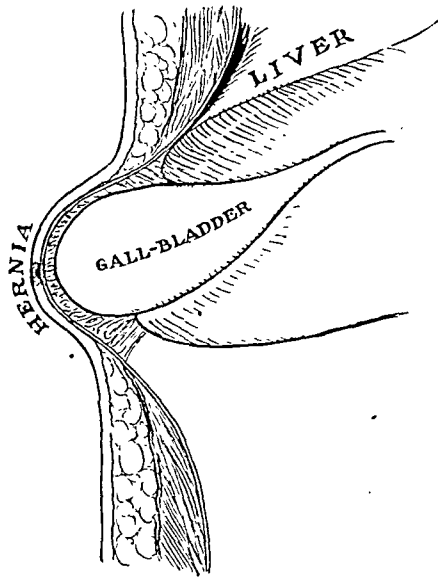


FIG. 15.—Case XXX. Hernia of gall-bladder. Adherent and somewhat distended gall-bladder in hernial sac.

6. DEVELOPMENT OF CARCINOMA IN THE RETAINED GALL-BLADDER. Although I have no personal experience with cancer developing after drainage of the gall-bladder, there are numerous reports in the literature of this occurrence (Fig. 16). Magoun and Renshaw,<sup>13</sup> in a recent paper from the Mayo Clinic on malignant disease of the gall-bladder, report 5 cases of carcinoma developing in the cholecystostomized gall-bladder in a series of 84 cases. In fact, it has even been shown that in many cases of inflamed gall-bladder, where this organ had been removed for what appeared to be merely an acute condition, there were pre-cancerous or actually outspoken malignant changes demonstrable upon microscopical examination. This in itself, even ignoring the possibility of the development of carcinoma later in the degenerated and retained gall-bladder, is one of the most potent arguments in favor of primary cholecystectomy.

7. **RECURRENT PANCREATITIS.** It is now generally conceded that both acute and chronic pancreatitis are usually traceable to primary disease of the gall-bladder with or without stones. The pancreatic lesion is the result either of direct extension through the ducts or of secondary infection through the lymphatics. In all probability, some of my cases, grouped under (4.) Recurrent Cholecystitis, had complicating inflammatory lesions in the pancreas, which were in part responsible for the various digestive disturbances. The early treatment of chronic pancreatitis with or without jaundice, due to compression of the papilla of Vater, was cholecystostomy. Although this operation was originally strongly advocated by the Mayos, they were finally forced to admit that the cure affected by the drainage of the gall-bladder was only temporary, and that a recurrence was likely through reinfection from the gall-bladder when the fistula closed. They<sup>16</sup>

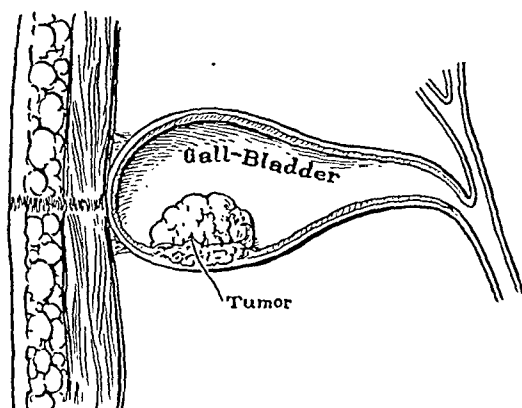


FIG. 16.—Carcinoma in the retained gall-bladder.

have since put themselves on record as advocating cholecystectomy as the only real curative procedure, primary in non-icteric and secondary in icteric cases.

8. **HEPATITIS.** Under this heading I would like to refer briefly to the possibility of an inflammatory invasion of the liver with attendant disturbances of hepatic function resulting from the retention of a chronically inflamed gall-bladder. Aside from the possible extension of an acute gall-bladder suppuration into the bile ducts and liver, a chronic hepatitis, especially of the right lobe, frequently exists, apparently as a direct sequel to a chronic cholecystitis, the inflammation extending into the liver either by contiguity or via the lymphatics, the portal vein or the biliary system. Heyd<sup>24</sup> has very recently emphasized this association in primary cases. It is clear that if this relation can be substantiated, the danger is quite as great in retained, chronically infected gall-bladders, no matter by what path the disease travels.



**II. The Difficulties and Disadvantages of Secondary Cholecystectomy.** Having seen the clinical results of retention of the gall-bladder, let us now turn to the other side of the question and see what the surgeon faces when he tries to correct the sin of omission on the part of the previous operator—in many instances, himself—and attempts a secondary removal of the retained gall-bladder.

I have subdivided the difficulties and disadvantages of secondary cholecystectomy as follows:

1. **ADHESIONS.** Probably because of the great vascularity of the organs in this region, it is well known that the adhesions that form after operation in the right upper quadrant of the abdomen are particularly dense and extensive and that secondary operations on the gall-bladder and ducts often try the skill and patience of the most expert and experienced. Frequently, the entire upper surface of the liver, or at least its edge, and the gall-bladder are virtually glued to the anterior abdominal wall. The omentum is usually firmly attached to the gall-bladder; the pylorus, duodenum and hepatic flexure of the colon are likewise involved and conditions are often so complicated that surgical entrance into the abdominal cavity and proper orientation are very difficult (see Cases III, IV, V, VI, X, XI, XIII, XIV, XV, XVI, XVII, XVIII, XIX, XXVI, XXVII, XXVIII, XXX and XXXI). This not only applies to secondary cholecystectomy, but also to other surgical procedures in the neighborhood of the gall-bladder (see partial gastrectomy, Case XIX).

2. **INJURY TO OTHER ORGANS.** A corollary to the difficulties encountered from the presence of adhesions, more dense and extensive than usual, is the accidental injury to other important intra-abdominal structures. In many cases, the separation of the gall-bladder from surrounding structures is practically impossible without some serious damage being done, no matter how carefully the operation is performed.

I need but to refer to Case XI, in which, in merely trying to re-drain the gall-bladder, the duodenum, which was densely adherent to the anterior abdominal wall, was inadvertently opened and drained, with eventually a fatal outcome (Fig. 17). This accident may have been avoidable, but, judging from the postmortem examination, if an actual cholecystectomy had been attempted, the gall-bladder was so shrunk and imbedded in adhesions that it would have been excessively difficult to locate it, and it was so adherent to the duodenum that an injury to that organ would have been an almost certain result.

In Case IV the duodenum and hepatic flexure of the colon were grown so firmly to the gall-bladder and under surface of the liver that only by the most careful sharp dissection could they be liberated, and the small, shrunk gall-bladder exposed (Fig. 18). It

seemed that this had been done with great success and without damage to the duodenum or colon, according to a very painstaking

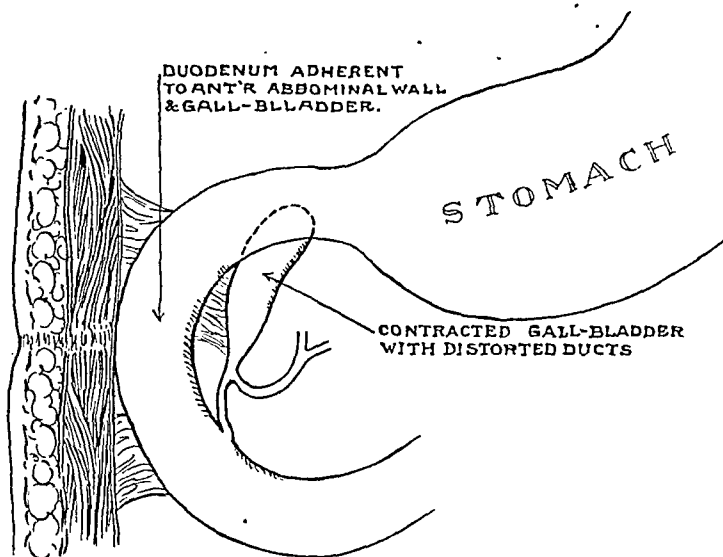


FIG. 17.—Case XI. Duodenum densely adherent to anterior abdominal wall and to shrunken gall-bladder. Distortion of ducts.

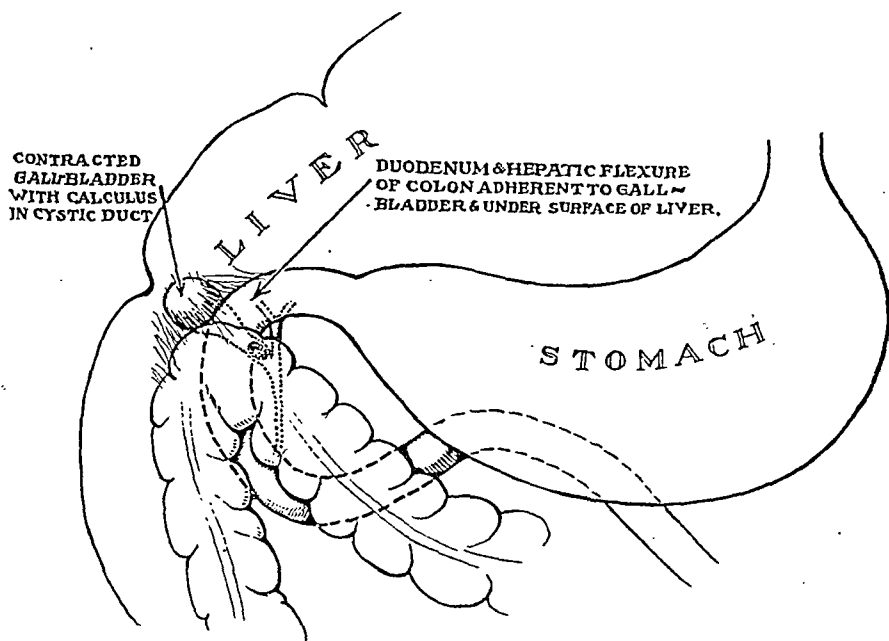


FIG. 18.—Case IV. Dense adhesions of duodenum and hepatic flexure of colon to gall-bladder and under surface of liver. Shrunken gall-bladder with impacted calculus in cystic duct.

inspection. Yet a week after operation, when the cigarette drain was removed, a fecal fistula of the hepatic flexure of the colon

developed. Although the development of this fistula was probably due, not to an actual operative perforation, but to erosion from the drains or invasion of the somewhat damaged gut wall by the infection, the primary cause and the end-result were the same. The fistula became mucocutaneous and required operative closure some months later.

In my series, it was my good fortune to have had no further accidents to other important abdominal organs. For the sake of completeness, however, I wish to emphasize the fact that, obviously, there is even much greater danger of seriously injuring the hepatic or common duct during one of these secondary operations, than at a primary cholecystectomy, where such injury is not an unusual occurrence.

3. **PROTRACTED OPERATION.** Although the usual primary cholecystectomy requires a half to three-quarters of an hour, because of the adhesions and the disturbed anatomy, the secondary operations are generally very tedious affairs. Even a speedy operator can rarely finish such a case in less than an hour and a half or two hours, and if the difficulties are particularly marked, a longer time may be required. This is not without significance in some of the cases, where the patients are much run down from long-continued illness, particularly in those cases that have had long-standing biliary fistulæ.

4. **HEMORRHAGE AND SHOCK.** Two other very serious factors are hemorrhage and shock, never to be regarded with indifference, but also of special seriousness in this class of cases. As already mentioned, the right hypochondrium is particularly vascular, and the bleeding in separating adhesions and loosening from the liver a firmly imbedded, shrivelled gall-bladder is often appalling. Frequently, the ligation of the cystic artery is next to impossible, and oozing from raw surfaces requires extensive tamponade (Cases V and XXVIII). This latter procedure, though necessary, predisposes to further adhesions, with the disadvantages that these entail. Unusual shock is an obvious sequence to the adhesions, protracted operation, additional operative traumatism and hemorrhage.

5. **POSTOPERATIVE VENTRAL HERNIA.** The possibility of the development of a postoperative ventral hernia is naturally increased by the relaparotomy. No comment is needed to explain this obvious fact. Case III is an illustration of this point. A large hernia has developed since the second operation, which will eventually require a third operation for its cure.

**Conclusions.** I think that it must be admitted from the observations that have been outlined, that it is justifiable to assume that the retained gall-bladder, at least one that has been drained, is a menace to the health, nay even to the life of the patient. Undoubtedly, some cases of cholecystostomy are cured,

but it has not been my fortune to have seen very many. The inference is obvious that if we operate on the gall-bladder—and it is more or less generally conceded today that gall-stones and most cases of cholecystitis, even without stones, should be treated surgically—then a primary cholecystectomy should be performed, if this is at all possible, irrespective of the degree of structural change in the gall-bladder itself. I would even go a step further. If, for any reason, either on account of the general condition of the patient or because of local difficulties, primary cholecystectomy cannot be performed and only cholecystostomy is done, this should be looked upon as an emergency procedure. A secondary cholecystectomy should be practised when the patient's condition has improved, unless there are specific contraindications. As a matter of fact, as can be seen from my experiences, reoperation is in many cases not a matter of choice but of compulsion. The one only exception to this rule is that mentioned in the beginning of this paper, namely, irremediable occlusion of the common duct, such as carcinoma of the head of the pancreas or impermeable stricture. Here the gall-bladder must be retained for the anastomosis with some part of the gastrointestinal tract. In chronic pancreatitis with jaundice, cholecystostomy should first be performed and, after the fistula has closed without symptoms so that the patency of the common duct is assured, secondary cholecystectomy should be undertaken. In chronic pancreatitis without jaundice, primary cholecystectomy is the operation indicated. In certain cases of so-called "silent" gall-stones, accidentally discovered during the course of a laparotomy for some other condition, where the gall-bladder is found to be comparatively normal, I have on several occasions practised "ideal cholecystotomy," closing the abdomen without drainage. This is at times a useful, alternate method, conserves the more or less healthy gall-bladder and obviates the disadvantages of cholecystostomy. Willis<sup>20, 21</sup> has very recently revived interest in this procedure and recommends it when indicated.

I have yet to see any harm come from the absence of the gall-bladder, in spite of the various theoretical objections that have been advanced against its removal. With very few exceptions, the many cases of cholecystectomy that I have observed have been promptly and definitely cured by the operative procedure, and never have I seen the slightest recognizable functional disturbance result from the loss of the gall-bladder, even when this organ was not seriously diseased at the time of operation. Where the gall-bladder is badly diseased, and particularly where the cystic duct is occluded, the gall-bladder is worse than functionless, anyway.

It has been said that one of the main objections to cholecystectomy is that there is a greater tendency to the formation of adhe-

sions. I believe the reverse to be the truth and that the retention of the diseased gall-bladder will produce many more and denser adhesions than its removal. I believe this to be particularly true with the technic which I am now using, with complete success up to date, and which has for some time been recommended by many, though not universally approved. I refer to cholecystectomy without drainage. I might here emphasize that the period of convalescence in cholecystectomy, particularly the wound healing, is much shorter than in cholecystostomy, and will be still further curtailed by this non-drainage operation. Incidentally, the complete closure of the abdominal wound without drainage is clearly not as feasible in secondary as in primary cholecystectomy.

May I conclude my plea for primary cholecystectomy with the statement that I agree with those surgeons who believe that the gall-bladder, found diseased at operation, should no more be left in the abdominal cavity than should the diseased appendix. Unless this maxim is followed, as a general rule, I feel that the surgeon will inexcusably place the future health, and even the life, of many of his patients in serious and unnecessary jeopardy.

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### ASSOCIATED ACUTE THORACIC AND ABDOMINAL DISEASE: WITH REPORT OF A CASE OF PNEUMONIA AND APPENDICITIS AT THE SAME TIME.\*

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NEARLY every hospital has the tradition of an early pneumonia being mistaken for an acute appendicitis because of abdominal pain and resistance. Operation revealed a normal appendix and a normal abdomen, and the case proved to be a frank pneumonia. An early pneumonia, with its accompanying acute fibrinous pleurisy with referred pain, may simulate any acute condition below the diaphragm. To put the point differently, abdominal pain and rigidity do not mean that there is abdominal disease, much less an acute abdominal condition. On the contrary, and under the same circumstances, it is often difficult to deny that acute abdominal trouble is present. Further, the laboratory offers practically no assistance in the differentiation, because there is usually a leukocytosis with high polymorphonuclear count both in pneumonia and in the acute abdomen.

In the following case, both a pneumonia and an appendicitis were present, and probably began at the same time, as the case is now viewed with the added accuracy of hindsight. The simple telling of the story will add emphasis to Pottenger's<sup>1</sup> recent statement that "Diagnosis is a process of reasoning." It shows the pitfalls in a concurrent acute abdomen and acute thorax. Truly, here, experience is fallacious and judgment difficult.

A well-developed girl, aged thirteen years, entered the Wesley Hospital on the afternoon of August 26, 1921, with a complaint of pain in the lower right abdomen. She had been well until August 11, when she developed a severe cold, which lingered until August 24,

\* Annual Oration on Medicine of the Medical Association of the State of Mississippi, May 10, 1922.

when she had a severe chill and high fever. In the afternoon of the next day, an acute epigastric pain developed and, on the day of entrance, it had localized in the right side of the abdomen, worse from above downward and culminating in the appendix region. On entrance, the subjective pain was greatest to the right of the umbilicus, though the entire right abdomen was resistant and most painful upon pressure over McBurney's point. Temperature, 103°; pulse, 140; respiration, 32. On account of her abdominal condition she was entered in the surgical service, and Dr. C. E. Dowman saw her at 5 P.M. His notes were as follows: "Percussion note definitely higher over lower half of right lung. Vocal fremitus slightly increased posteriorly right. Breath sounds: Expiratory sounds rather prolonged and somewhat harsh over lower right side. Abdomen: Marked tenderness over right lower quadrant. No mass felt. Hyperesthesia test absent. Impression: Case is probably one of the right lobar pneumonia with referred pain in the appendix region. A true appendicitis, however, should be kept in mind. Have internist see patient."

My notes after examination, one hour later, were as follows: "Patient has a tachypnea of 36, rhythmic; pulse, 128. Absent to decreased fremitus midright scapula downward, increased above. Squeaking rales, rhonchi, few fine crepitant rales fifth space anteriorly outward and backward to right back. Acute fibrinous pleurisy, probably right anterior axillary line. Referred abdominal pain. Cold preceded illness. Would suspect frank pneumonia signs by morning."

Her urine was 1026, with a heavy trace of albumin. The leukocyte count was 17,600; polymorphonuclears, 83 per cent; small lymphocytes, 15 per cent; large lymphocytes, 2 per cent. An ice-bag was kept constantly on the right lower quadrant. On the next day, August 27, a bronchopneumonia, involving the entire lower right lobe was present, and the abdominal pain and rigidity were greatly decreased. The abdominal improvement was interpreted as a result of the ice-bag and the care of the patient. Now, we believe it was due to the rupture of the appendix. Coughing had begun. Temperature ranged from 99° to 101°; pulse, from 88 to 110; respiration, 20 to 24. On August 29, she complained of pain in the entire abdomen, with increased pain on pressure over the appendix and upward. On August 30, coughing gave her abdominal pain, and by 8 P.M. it had localized in the lower right quadrant. On August 31, the abdominal pain was more severe; epistaxis occurred and vomiting, with a few blood streaks. The cough accentuated the pain, but it was clearly evident that there was an abdominal lesion as well as a pneumonia. The hyperesthesia test, elicited by drawing a pin over the abdomen, gave a pronounced reaction over the appendix region. The progress of the pneumonia was satisfactory and her general condition fair. On

September 2, the leukocyte count had dropped to 7000, with a normal differential count. The patient looked better, temperature and pulse were normal and respiration was 26. Right lower quadrant rigid; decided localization, with mass sensation upon palpation over cecum. Breathing all thoracic. Operation was done at once under local anesthesia, and a large walled-off retrocecal appendiceal abscess was found. The appendix was not removed. Stab drainage in right flank. Morphia was necessary to relieve the abdominal pain from the cough of the pneumonia. Patient was septic with continued fever, rapid pulse and prostration. Calomel was given on September 5 and 6, with much improvement. Temperature, pulse and respiration were normal on September 8. Recovery uneventful thereafter.

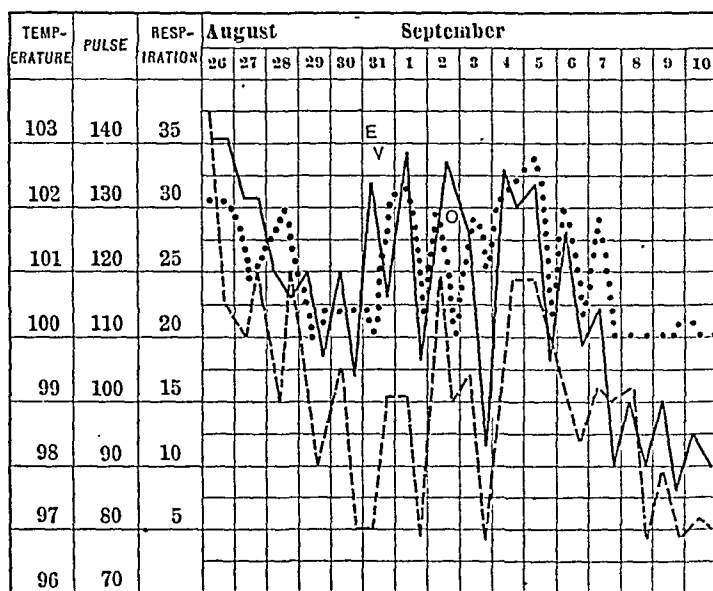


FIG. 1.—Solid line, temperature; broken line, pulse; dotted line, respiration; V, vomiting; E, epistaxis; O, operation.

There is evidently much more to this case than a simple case of pneumonia or appendicitis. The patient had a severe cold for thirteen days, and then suddenly had a chill and fever, with signs of pneumonia and appendicitis. We believe both began at the same time, and that they were the local manifestations of a general septicemia. Had there been no lung signs, the diagnosis would have been acute appendicitis. In the beginning, we thought the abdominal condition was due to the referred pleural pain of the pneumonia. Unfortunately, a blood culture was not taken. The sputum and pus from the appendiceal abscess both contain staphylococci and short chain streptococci. No pleural friction rub was ever heard. The abdominal pain began in the epigastrium.



even though the appendix was retrocecal. The abdominal pain was probably due entirely to the appendicitis and there was probably no referred pain from the thorax at any time.

Cabot's case record No. 7363 (Massachusetts General Hospital), is an account of a similar case, except that the appendix seemed the only organ involved. It was removed, but a right bronchopneumonia was at once evident and a mild jaundice as well. At necropsy, there was a fibrinous pleurisy and a fibrinous pericarditis. Here was a blood-stream infection, a bacteriemia, that was the beginning of the pathological mischief in lung, appendix, liver and pericardium. The pneumococcus was the "criminal." Cabot wisely

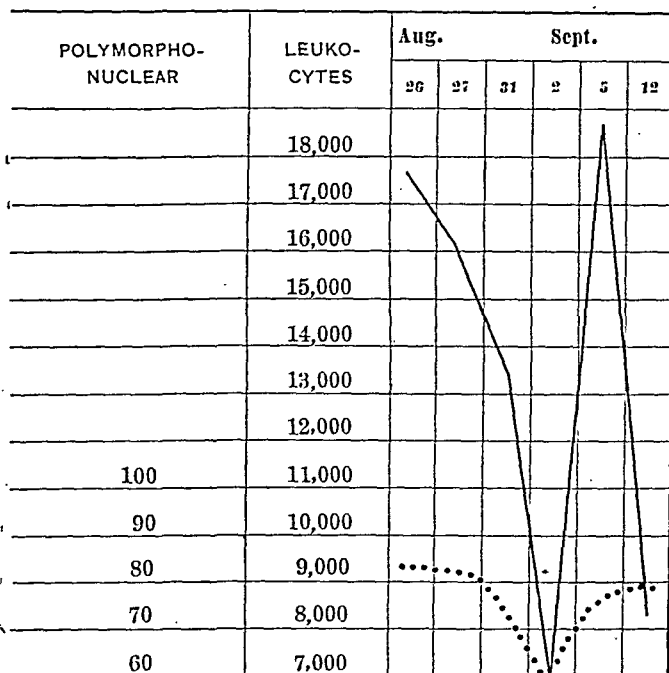


FIG. 2.—Solid line, leukocytes; dotted line, polymorphonuclear leukocytes; operation, September 2.

says, in discussing this case, "I believe we shall see a great deal more of the doctrine of general septicemia, with local manifestations or without." W. W. Herrick<sup>2</sup> has shown that epidemic meningitis is preceded by a general invasion of the blood stream, or stage of meningococcic sepsis, and that in some cases the infection remains a sepsis and never localizes in the meninges or elsewhere. It is significant that measles, meningitis and influenza are so often complicated by bronchopneumonia. We saw one soldier who had measles, meningitis, bronchopneumonia and erysipelas, in the order named (the last three concurrently), and he recovered. In Cabot's case and in ours, the pneumonia was bronchial in type.

Two recent cases bear upon general sepsis: a little girl, aged seven years, had chronic infectious tonsillitis, endocarditis with mitral incompetency, acute rheumatic fever and chorea major at the same time. She recovered with, of course, a damaged mitral valve. A woman, aged forty years, had an acute suppurative cholecystitis with a polyarticular arthritis, and the arthritis disappeared after a tonsillectomy and a cholecystectomy. Bindi<sup>3</sup> reports a case of acute arthritis associated with an acute appendicitis.

We have, in recent years, been so overwhelmed with the importance of the doctrine of focal infections, and so intense in the search for the focus, that we have probably not accentuated sufficiently the importance of the blood stream in the dissemination of the bacteria, whether known or unknown. Ports of entry of focal infections through the blood stream to the tissues are of two kinds: (a) Peripheral and relatively easily demonstrable foci, as the teeth, tonsils, mouth, sinuses, skin, cervix, urethra and prostate; (b) cryptic foci, relatively impossible to demonstrate, as the mucosa and alveolar cells of the bronchial tree and the intestinal mucosa. The hidden potential foci are far more numerous than the peripheral foci. In either case, the blood stream may be a culture medium for bacterial growth as well as a distributing agent for the elective localization of the bacteria in different organs. It is meningococcic sepsis when the meningococci remain in the blood; when they localize in the meninges, it is meningitis. In the case reported, the bacteria probably localized in the lung and appendix after a stage of sepsis, following entrance from an unknown focus. Hidden sepsis is a phrase of no mean value and emphasizes the importance of careful and repeated blood cultures. General sepsis may be present without pus, or discoverable focus, or port of entry into the blood stream, once the bacteria enter the closed circulation. The blood stream does the rest, with or without subsequent localization.

The doctrine of referred pain is one of ever increasing importance. Here was an acute abdominal condition that was taken to be a referred pain from acute thoracic disease. We have so fallen into the use of instruments of precision in the study of a case, that we may overlook the precision of referred pain or overestimate it entirely. James MacKenzie's book on *Symptoms and Their Interpretation* should be familiar to every clinician. There is enough time in every case of appendicitis to be sure it is appendicitis, and not a referred pain.

A few simple facts are of aid in reaching a conclusion in a problem of referred thoracic pain: The lungs give rise to no sensation of pain. The pleura is insensitive to probing or stimulation. The pain in a pneumonia, whether local or referred, is due to the involvement of the pleura, usually as an acute fibrinous pleurisy. Little is known of the nerve supply to the pleura. The intercostal

muscles over the affected lung are tender upon pressure in a painful pneumonia chest. "The most severe pain occurs in the movement of respiration and is due to the peripheral contraction of the intercostal muscles" (MacKenzie). The intercostal muscles over a painful pneumonia are in a state of rigid contraction. The pain is often localized in the anterior axillary line, where the visceral, parietal and diaphragmatic pleura make their maximal excursion. The pain may be referred to the abdomen reflexly through the intercostal nerves.

The skin and muscles of the abdomen are supplied by the anterior branches of the six lower dorsal nerves and the ilioinguinal and the iliohypogastric from the lumbar plexus. The intercostal muscles of the thorax are supplied by the second and third cervical and the second, third and fourth dorsal; the diaphragm by the phrenic from the fourth and fifth cervical. The spasm of the intercostal muscles is a visceromotor reflex—pleura to cord to intercostal muscle. The pain in the chest is a viscerosensory reflex, due to the painful contraction of the muscle on its contained nerves—pleura to cord to muscle.

Both the abdominal muscles and the skin overlying them are supplied by the spinal nerves. The referred pain in a pneumonia is, therefore, a viscerosensory reflex—from pleura through thoracic intercostal nerves to cord, and then a shunting down the cord to the lower dorsal nerves to abdominal skin, and painful nerves in contracted muscles. The pain in diaphragmatic pleurisy is a viscerosensory reflex to the shoulder crest. The referred pain in acute thoracic disease may localize in the upper abdomen and simulate gall-bladder disease or ruptured gastric or duodenal ulcer. To further complicate the problem, referred pain may shift up and down the abdominal wall.

The spinal nerves supply the surface, and the sympathetic the viscera beneath the surface of the abdomen. The hyperesthetic, painful, resistant or rigid abdominal muscles in appendicitis are entirely due to reflex action. The cold hand upon the warm abdomen causes instant contraction of skin and underlying muscles.

Pain in the epigastrium in gall-bladder disease or umbilical region in appendicitis seems to appear there because these parts are derived from the primary embryological median tube and peristaltic pain also is usually referred to the median line. The nerves to the appendix are from the mesenteric plexus, and are intimately connected with the dorsal and lumbar spinal nerves. In appendicitis, there is reflexly a visceromotor reflex with spasm of the erector spinæ in the right flank and spasm of the psoas with tendency to flex the right thigh.

**Conclusions.** 1. In concurrent acute thoracic and acute abdominal disease, it is very difficult to separate the signs and symptoms of one from the other, on account of the doctrine of referred pain.

The laboratory is of little assistance. It is a matter of clinical judgment.

2. Even an early pneumonia, through referred pain to the abdomen, may simulate any acute condition below the diaphragm, and yet the abdomen be normal. Hesitancy here and observation are of value.

3. Acute concurrent inflammations, as illustrated by the case reported, in different organs or different systems of organs intimate a blood-stream infection, and the acute diseases are its local manifestations.

4. No acute abdominal trouble should be operated upon until a real examination of the lungs has been made. Where there is a doubt between the acute thoracic and the acute abdominal condition or both concurrently, a policy of watchful clinical waiting is in order. If still an operation seems imperative, local anesthesia will probably lessen the thoracic danger.

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### PRIMARY LYMPHOBLASTOMA OF THE STOMACH.

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TUMORS of the stomach, carcinoma excepted, are comparatively infrequent. The term lymphosarcoma signifies a malignant tumor of mesenchymal origin in which the tumor cell is of the lymphocyte series. Lymphosarcoma may occur anywhere in the lymphatic system (including the lymphoid tissue of the gastric wall). A rational division of lymphosarcoma is into: (1) A group of cases in which the predominating type cell is the small round cell which corresponds to the lymphocyte of the circulating blood; and (2) a group in which the predominating type cell is not the lymphocyte but its ancestral element—the larger, more cytoplasm-rich, hyperchromatic lymphoblast as it occurs normally in the germinal centers of lymph nodes. To the first group the name *lymphocytoma* may be applied; to the second group is applied the name *lymphoblastoma* (Ribbert,<sup>1</sup> Delafield and Prudden<sup>2</sup>). Some cases of lymphosarcoma clearly belong to the first of these groups and other cases clearly to the second group, but between the two rather

clear-cut extremes there are overlapping cases—cases in which there is such a free admixture of smaller cells approximating lymphocytes and of the larger and more immature lymphoblasts that satisfactory classification may not be possible. Ribbert would discard the term lymphosarcoma as applied to either group, reserving the term sarcoma for tumors of supporting connective tissue. By pathologists in general the tendency is to include also under the name of lymphosarcoma the tumor masses of lymphatic leukemia and Hodgkin's disease. Pathologists in general have not accepted the views of Frankel and Much, Bunting and Yates, Rosenow and others as to the bacterial origin and granulomatous nature of Hodgkin's disease. On the contrary, the drift of opinion is to the view that Hodgkin's disease is essentially neoplastic (lymphosarcomatous) in nature.

The literature of primary lymphosarcoma of the stomach is scant, and in case reports very few, if any, attempts have been made to draw a line between lymphocytoma and lymphoblastoma. There are in the Surgeon-General's Library clinical or autopsy reports in German by Török (1892)<sup>3</sup>, Sternberg (1907),<sup>4</sup> Saltikow (1910)<sup>5</sup>, Ruppert (1912),<sup>6</sup> and Krabbel (1918).<sup>7</sup> Török's case was in a woman, aged twenty-one years, in whom almost two-thirds of the stomach and three regional glands were removed. The tumor was the size of a fist involving the greater curvature toward the fundus and densely adherent to the parietal peritoneum. The patient was seemingly well nearly two months after operation. Sternberg comments upon the almost universal rule of dilatation of the stomach in the presence of lymphosarcoma. In Saltikow's report of 3 autopsies, all in elderly women, (aged sixty-seven, sixty eight and seventy-four years), the stomach was normal in size in 1 and reduced in 2.

Ruppert's interesting report is of a case in a woman, aged seventy-two years, in good health, for whom he had done a nearly complete gastrectomy fourteen years previously. The movable tumor was as large as a child's head and occupied almost the whole length of the stomach except a strip of three fingers' width at the fundus. There were also numerous glands involved in the great and small omentum and at the cardia. The wall of the stomach was infiltrated in almost its entirety. Ruppert comments upon the extreme malignancy of lymphosarcoma and states that he could find in all the literature but 12 operated gastric cases, of which 5 died from the operation and of the remainder none had survived as long as his case.

Krabbel's report is of a case autopsied after exploratory laparotomy for acute *dynamic* intestinal obstruction. The whole fundus and the lesser curvature were extensively infiltrated and there were two ulcerated areas, but the pylorus was not obstructed. Metastases were very extensive. The brain and cord were not

examined, but cerebral symptoms clinically resembling those of bulbar paralysis strongly suggested metastases in the central nervous system. The immediate cause of death was considered to be sudden heart failure due to myocardial metastases. Krabbel calls attention to the infrequency of primary lymphosarcoma of the stomach, stating that Pappert in his thesis in 1911, could find but 26 cases in the German and foreign literature. Krabbel believes that the disease runs a long symptomless course prior to the onset of serious symptoms, for which reason early operations and operative cures have been rare. He states that pyloric stenosis is extremely rare. He also observed that in a majority of cases reported cachexia was completely absent or appeared late and suddenly. In his case the patient, a teamster, continued at his duties until within less than a month of death.

Reports of but 2 cases in French could be found, 1 by Ferlin (1907)<sup>8</sup> in a man, aged forty-seven years, who for a long time had complained of stomach symptoms with hemorrhage now and again and in whom there eventually developed a phlebitis in both legs; the other by Gilbert (1912)<sup>9</sup> in a man, aged fifty years, who also had hemorrhage. Both cases were autopsied and examined histologically.

Only 2 cases could be found in English literature, reported by Hadden (1886)<sup>10</sup> and Alson (1886)<sup>11</sup>.

American literature is likewise limited: in 1862, Jackson<sup>12</sup> showed an undiagnosed postmortem specimen described as "a very anomalous tumor found in the parietes of the stomach," a detailed account of which suggests primary lymphosarcoma. This case appears to be the first recorded.

Scott and Forman (1916)<sup>13</sup> reported a case of diffuse gastric neoplasm with metastases in the lymph nodes along the lesser curvature and about the head and along the upper margin of the pancreas, which was studied histologically and classified as Hodgkin's disease of the stomach.

Broders and Mahle (1921)<sup>14</sup> reported 12 cases of primary lymphosarcoma of the stomach occurring in the Mayo Clinic from January 1, 1913, to December 1, 1920. According to their records (Mayo Clinic) primary lymphosarcoma of the stomach as compared with carcinoma occurs in the proportion of 1 to 68; 11 of their cases were in males. The age limits were from sixteen to sixty-two years. The clinical diagnosis in 7 was carcinoma; the remaining 5 were variously diagnosed, but not one as lymphoblastoma or sarcoma.

In a private communication of February 23, 1921, F. B. Mallory states that during the past twenty-five years there have been but 3 cases of lymphoblastoma of the stomach in the Boston City Hospital.

Lymphoblastoma of the stomach is very malignant, as would

be expected in view of the large cytoplasmic content and immaturity of the component cells. The tumor grows rapidly and tends to infiltrate extensively. In microscopical slides numerous mitoses are apt to be seen, especially in metastases. In nearly all, if not in all, of the autopsied cases, extensive metastases have been found—in some cases so generalized as to involve most of the organs of the body. The regional lymph nodes are most frequently and first involved, but other nodes, the omentum, mesentery, intestine, liver, spleen, pancreas, kidneys, diaphragm, pleuræ and heart are apt to suffer. It is probable that even the central nervous system may be invaded. Metastasis occurs through the lymph current and, it may be, in some cases also through the blood current.

The clinical diagnosis is difficult. In a review of all case reports available, I did not find a single case in which the clinical diagnosis was made. The usual diagnosis was carcinoma. In its early stage the tumor is most frequently situated in the pyloric end and upon chemical analysis of the gastric contents the findings are like those of cancer.

Some clinical features which may have a diagnostic value are: (1) The age of the patient. A considerable percentage of the reported cases has been in patients too young for carcinoma. (2) The absence of pyloric stenosis. In several of the cases reported the absence of obstruction was noted. In the case below reported, although the primary tumor was very close to the pylorus, the outlet was not notably narrowed; and although after gastro-jejunosomy, metastasis occurred proximal to it, the ring was not encroached upon; and although the distal end of the esophagus became seriously involved, its lumen was not obstructed. (3) Absence of cachexia or its very late appearance. This fact was also commented upon in some of the case reports. (4) A greater tendency in some cases to copious bleeding than ordinarily is present in carcinoma. (5) Possibly a period of more or less prolonged ill health prior to the onset of severe symptoms. Krabbel called attention to this feature.

It is quite likely that primary lymphosarcoma of the stomach is not as rare as the literature would indicate; the Mayo Clinic records tend to this conclusion. Doubtless many cases of gastric tumor diagnosed as carcinoma would have proved to be lymphosarcoma if studied histologically.

In the case to be reported presently it seemed to me that it might be of some interest to apply to the patient's serum the specific ferment test (dialysis procedure) of Abderhalden, the object being to determine whether in case of a positive reaction to a fragment of the patient's own tumor (to be obtained at autopsy), there would occur a similar reaction to such other tumors of the lymphocyte series as it might be possible to secure. Accordingly blood was

taken by Dr. O. B. Hunter five days before death and the serum preserved under proper conditions. Dr. Hunter kindly consented to make the tests in his laboratory at the George Washington University Medical School. Unfortunately the only additional material which could be obtained during the period of activity of the serum was a fresh fragment of lymphocytoma sent to me by Dr. L. F. Barker. The two tumors reacted positively, that is, showed the presence of a defense ferment, which correspondence tended to establish their serological identity as well as to confirm their close pathological relationship.

As to the prognosis little need be said except that the only cured case which I could find of record was the case of Ruppert previously mentioned. Doubtless the problem of cure is more or less analogous to the problem of gastric cancer, if the disease were recognizable in its incipency and were dealt with radically there would be more cures.

**CASE REPORT.** F. W. T., aged sixty years; lawyer; American; married; resident of Washington, D.C.

*Family History.* Negative for malignant disease.

*Previous Personal History.* (September 22, 1919.) No serious illness or injury during adult life and health excellent, with average weight of 175 pounds, until last two years; during past two years mild dyspeptic symptoms from time to time—capricious appetite, with eructations of gas and flatulency; no pain, nausea, vomiting or diarrhea; mildly constipated at times; during same period gradual loss of weight, in all about 30 pounds, and diminishing endurance; otherwise general health satisfactory and there has been no interruption of work; habits always temperate.

*Physical Examination.* Height, 5 feet 10 inches, weight, 147 pounds. Head and neck negative except for some suspicious teeth—tonsils appear normal; chest negative except for slight enlargement of heart to left and moderate accentuation of second aortic sound; abdomen of normal contour, everywhere soft, no tenderness, no palpable mass; liver not palpable below normal limits; spleen not palpable; regions of pylorus, gall-bladder and appendix negative; kidneys in good position; peripheral arteries moderately stiffened; blood-pressure 105 to 186; a few palpable lymph nodes in either groin; temperature normal; general appearance that of moderate malnutrition and a moderate degree of anemia.

Blood examination, erythrocytes, 4,400,000; leukocytes, 7600; hemoglobin 78 per cent; Wassermann, negative. The morning urine showed no indican or other abnormality. The stool was well digested and showed no excess of mucus and no gross or occult blood, parasites or ova.

Roentgen-ray examination of the upper digestive tract (Christie, September 24, 1919): abscesses involving roots of upper left first



molar and very marked pyorrheal absorption about all lower incisors; the stomach is ptotic, but normal in contour, motility, mobility and time of evacuation; no deformity of pylorus or duodenal cap; no shadows of gall stones or other evidence of gall-bladder disease.

A diagnosis was made of oral infection and a moderate general arteriosclerosis.

The patient was not seen from September 26, 1919, to April 29, 1920.

*Condition April 29, 1920.* The symptoms since former examination have been in the main a continuance of those previously present, except that recently there has been a more rapid loss of weight. The general condition has greatly deteriorated—the patient is thin and sallow, but not distinctly cachectic; weight 132 pounds. Examination of abdomen shows the presence of a definite, firm, tender mass in the region of the pylorus about the size of a small orange cut in two transversely, which moves to and fro with excursions of the diaphragm. Gastric contents: complete absence of free hydrochloric acid, total acidity 5, a trace of lactic acid and a small amount of gross blood. The stool shows occult blood. A diagnosis of pyloric carcinoma seems probable. Although the tumor is obviously very close to, if it does not actually involve, the outlet, there is no evidence of obstruction—solid food is taken without a great deal of discomfort and there has been no vomiting.

Roentgen-ray examination of stomach, May 5, 1920 (Christie), shows a large filling-defect involving the pyloric end, considered to be typical of carcinoma.

The patient was admitted to the George Washington University Hospital, May 8, 1920, and two days later the abdomen was opened by Dr. William C. Borden. A firm, circumscribed, somewhat nodular gastric tumor approximately 7 by 8 cm. in size was found, involving both curvatures and both walls and reaching very close to, though not involving, the pylorus. There were two moderately enlarged gastro-colic glands; otherwise no discoverable metastases. The liver and pancreas appeared normal. A posterior gastro-jejunostomy was done with the anastomosis as far away as practicable from the growth. Recovery from operation was excellent. Fifteen days after operation roentgen-ray examination showed an almost empty stomach one hour after the barium meal, evacuation taking place entirely through the ring of the anastomosis. Sixteen days after operation the abdomen was again opened by Dr. Borden. The tumor had increased considerably in size; its rate of growth was impressive. Something more than the distal third of the stomach with the proximal end of the duodenum and the two enlarged gastro-colic glands were removed *en masse*. It was possible to make the gastric incision well away from the tumor-mass without encroaching unduly upon the opening of the gastro-enterostomy. The stomach wall beyond the limits of the

mass did not seem to be infiltrated. The operative diagnosis was carcinoma. The operation was well borne and recovery uneventful. On June 6 (twelfth day after gastrectomy), the patient was returned to his home in remarkably good condition, although his weight had dropped to 117 pounds. From then he ate well and with complete comfort and gained weight rapidly. Blood examination July 31: Erythrocytes, 4,200,000; leukocytes, 6500; hemoglobin 66 per cent (Dare); polymorphonuclears, 70 per cent; lymphocytes, 23 per cent; mononuclears and transitionals, 3 per cent; eosinophiles 3 per cent; myelocytes, 1 per cent; red cells show considerable achromia, moderate anisocytosis, moderate poikilocytosis and some tendency to polychromatophilia in an occasional cell; no nucleated reds. On September 17, the weight was 134 pounds, or 2 pounds more than preoperative weight.

*Note of September 20:* General appearance fair; above navel to left of median line there is a doubtful small mass; liver, spleen and lymph nodes, other than those in groins, negative.

*Note of October 21:* Appetite poor, not much gas, no nausea or vomiting; complaint of pain and tightness in lower part of chest—no cough; tongue clean; pulse rate, 96; temperature, 101.5°; impairment of resonance, diminished breath sounds and moist rales over bases of lungs; mass previously noted as doubtful is now easily palpable between left costal margin and navel, quite firm, movable.

On October 24, there were many evidences of severe hemorrhage: Pallor, rapid pulse, subnormal temperature, cold extremities, an attack of syncope on rising, and so on. The general condition rapidly went from bad to worse. On two or three occasions some moderately bright blood was vomited and there were some black stools. Death occurred October 27, five months and one day after gastrectomy and approximately thirteen months after stomach had been found normal on physical examination and radiographically. The immediate cause of death was massive hemorrhage.

**PATHOLOGY.** 1. *Specimen Removed at Operation.* The specimen consists of distal portion of stomach, proximal extremity of duodenum and a portion of gastro-colic omentum. Dimensions of gastric portion containing tumor are 14.5 cm. in length by 8.5 cm. in width, with a capacity of 250 cc. The neoplasm involves anterior and posterior surfaces and both curvatures. The two surfaces and inferior curvature are extensively thickened, hard and nodular; the superior curvature is also thickened, but to a less degree. In the omental portion of specimen there are two moderately enlarged lymph nodes and several nodes of smaller size. The gross specimen is suggestive of a diffuse infiltrating carcinoma. After fixation in 10 per cent formalin the infiltrated walls are very friable and fracture easily on traction or bending. The nodular infiltration involves all coats from mucosa to peritoneum,

but without breaking through the latter. On the mucous surface there are a number of undulating projections, hard and firm, with numerous small grayish nodules—the whole covered with a brownish-black, flaky exudate. There is no ulceration. On the external aspect there are similar wavy projections, but none of the smaller nodulations; the peritoneal coat is comparatively smooth.

The tumor cuts with firm uniform consistency and appears as a white solid growth involving the entire thickness of the gastric wall, with complete obliteration of the outlines of the mucous, connective tissue and muscular tunics. The entire growth appears to be well distal to the line of amputation. The excised glands show on section the same white uniform appearance and firm consistency.



FIG. 1.—Microphotograph showing lymphoblastic growth infiltrating and obliterating gastric glands.

Microscopical sections from central part of growth show extensive lymphoblastic proliferation, completely obliterating the mucous, submucous, and muscular coats, with absolute loss of all of the normal histological structures. The thickness of the growth varies from 5 mm. to 20 mm. Toward the periphery the lymphoblastic growth shows macroscopically a rather sharp line of demarcation between it and the normal mucous membrane and musculature, but microscopically there is a well defined diffuse, but scanty, lymphoblastic infiltration into these coats as well as the submucosa.

Cytological study shows a great predominance of large hyperchromatic, lymphoblastic cells, atypical in arrangement and structure, closely packed together, with little supporting connective

tissue. There are no distinct giant cell formations, although there is some tendency to nuclear group accumulations with little



FIG. 2.—Microphotograph showing lymphoblastic growth infiltrating and obliterating gastric musculature.



FIG. 3.—Microphotograph showing left gastric artery with perivascular infiltration only. *a*, lumen of vessel; *b*, media; *c*, adventitia, showing lymphoblastic infiltration.

cytoplasmic production. A few eosinophiles are found scattered through the tumor in various areas. Some lymphocytes are pres-

ent with small round pyknotic nuclei and little cytoplasm, but are comparatively scant. Endothelial proliferation and fibroblastic formation are at a minimum. New-formed capillaries are moderately abundant and there are many vascular spaces with no apparent endothelial lining. Some polymorphonuclear leukocytes are found in the tissue, but are not numerous; they are found more particularly toward the mucous surface and in the regions of the larger capillaries. Numerous mitotic figures are found throughout the mass and there is extensive hyperchromatosis of the lymphoblastic nuclei.

Sections from the lymph nodes show essentially the same histological structure as the primary growth.

2. *Partial Autopsy (Incomplete for Lack of Consent) Done Three Hours After Death.* Stomach, liver (both lobes), omentum, proximal part of jejunum (region of gastro-enterostomy) and a large part of the transverse colon are densely adherent to parietal peritoneum in line of operative incision and bilateral to it. The gall-bladder is incarcerated in a mass of adhesions. The proximal part of lesser curvature of stomach, the proximal part of the lesser peritoneal sac and the transverse fissure of the liver are filled with adhesions and new growth. There are many enlarged abdominal lymph glands including the paracardial, superior gastric, hepatic and pancreatocolic groups. No enlarged pyloric or inferior gastric glands can be found. Removal of these groups appears to have been completely effected by operation. The retroperitoneal glands do not seem to be involved. Both lobes of liver and the pancreas contain new growth. The spleen, although firmly attached to the stomach, contains no gross mass. By palpating through incision in diaphragm, glands of the posterior mediastinum are found enlarged and nodules are felt in left lung in region of hilus.

Examination of stomach after removal shows perfect healing of distal extremity (line of amputation) without macroscopical evidence of recurrence of growth in that vicinity. The ring corresponding to surgical junction of stomach and jejunum is 3.5 cm. in its longest diameter and is covered with apparently normal mucous membrane. The stomach and small and large intestine contain a very large volume of fluid and clotted blood. At the proximal end of the superior curvature of the stomach is a hard mass 6 cm. in length by 2.5 cm. in thickness, from which there is a well-defined extension upward involving the right lateral wall of the lower end of esophagus. The esophageal lumen is not appreciably narrowed. From the distal portion of the mass, but reaching close to the proximal end of the superior curvature, there is another extension hanging in a more or less pedunculated manner into the cavity of the stomach. In the latter extension the distal portion of the left gastric (coronary) artery is found with numerous

eroded branches from which very extensive bleeding has occurred. The remaining portions of the stomach show no evidence of neo-

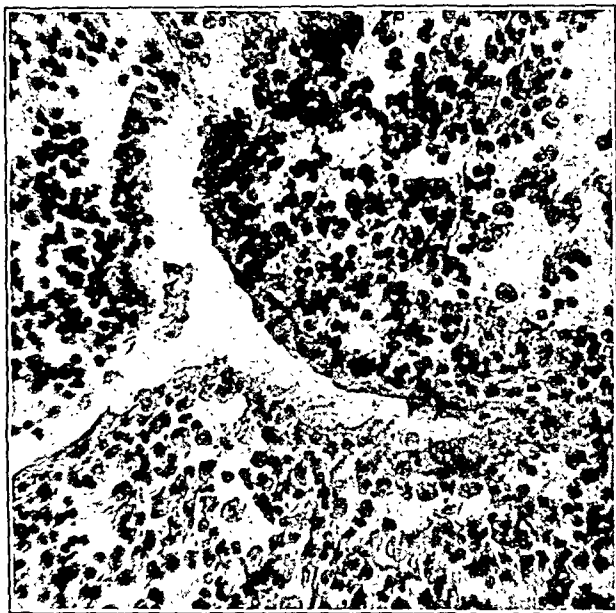


FIG. 4.—Microphotograph from operative specimen, showing rich, lymphoblastic growth and embryonic bloodvessel.

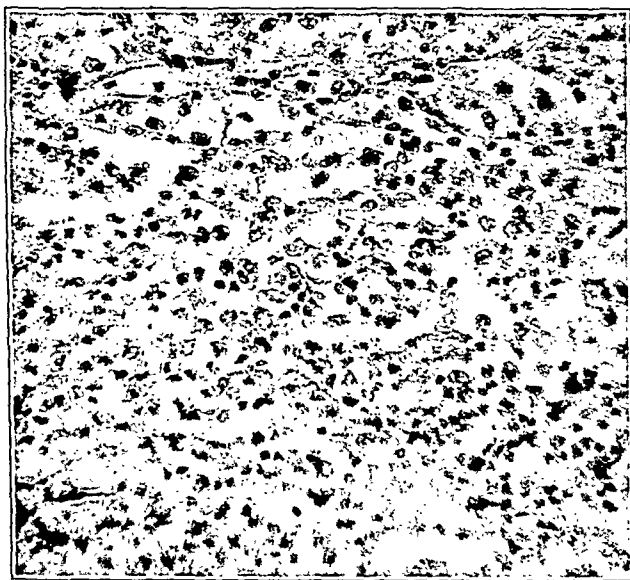


FIG. 5.—Microphotograph from autopsy specimen, showing same richly cellular growth with mitotic figures, similar to operative specimen.

plasm and no nodules can be found in the distal portion of the jejunum, the ileum or the colon. The mass in the stomach clearly represents the initial recurrence. The masses in the liver

and pancreas appear to be direct extensions. The numerous metastases noted (*e. g.*, in the mediastinal glands) have obviously occurred through the lymph current.

Microscopical sections from various specimens show essentially the same lymphoblastic proliferation and infiltration as the operative specimen. Curiously the trunk of the left gastric artery is surrounded by the growth, with some infiltration of the adventitia, but without involvement of the media and without obstruction of its lumen; some of its smaller branches are eroded. A few nerves in the immediate neighborhood show some infiltration of the epineurium, but no invasion of the medullary structure.

The pendulous mass in cavity of stomach consists of fibrin, lymphoblastic and polymorphonuclear infiltrations, some connective tissue and many bloodvessels. The latter show evidence of extensive hemorrhage and are the seat of fatal bleeding. The outline of some of the lower mediastinal glands can only be made out by their pigmentary deposits and capsule ghosts.\*

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### NON-SPECIFIC GRANULOMATA OF THE INTESTINE.†

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OUR purpose in this paper is to describe the pathological and some of the clinical features of a malady which, we have reason

\* I am greatly indebted to Dr. O. B. Hunter for his careful examination of specimens. The pathological study is his.

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to believe is not uncommon, and yet, as far as we are aware, is not widely known in this country. Its recognition thus far seems to have been confined to European observers. Its literature, strangely enough, covers but little more than the past decade, is almost entirely casuistic and concerned more with the clinical phases rather than the pathological. Even before this period descriptions of this lesion are by no means uncommon, but under the designation of "hyperplastic tuberculosis of the intestine" or syphilis. With a more rigid histological critique we believe this lesion can be partitioned from the large group of specific intestinal granulomata. Its interest is not entirely morphological. It is important clinically and is a malady which both the clinician and surgeon must consider in dealing with obscure tumors of the abdomen. The cause, with exceptional instances, is thus far unknown.

**Case Reports.** CASE I.—J. K., male, aged twenty-three years.

*Family History.* Father died of pneumonia; two sisters and one brother living and have always been well.

*Previous History.* The patient had measles, whooping cough, scarlet fever and pneumonia as a child. No rheumatism.

*Present History.* In December, 1917, the patient was first seen by one of us. He had a diarrhea averaging seven to eight movements a day for the past year. The stools were soft and occasionally tinged with blood; no cramps. He was a thin (112 pounds), pale somewhat anemic boy. There was a short presystolic murmur at the apex. The abdomen was lax, flat; no tenderness or mass. Under diet, etc., treatment and salol he improved so that he had but two or three fairly well formed movements a day. There was steady gain in weight (119 pounds). In May, 1918, he was operated upon for a typical attack of acute suppurative appendicitis from which he made a perfect recovery. In November, 1918, he had pain in the right iliac fossa. The bowels moved three or four times daily. A mass was found in the right iliac fossa, the size of a peach, firm, circumscribed and moderately tender. There was no fever. Weight has come down to 112 pounds. The condition remained practically stationary until February, 18, 1919, when he was operated upon by Dr. Wilensky. The cecum was found to be the seat of a hard firm mass. A resection was done with an end-to-side anastomosis. A fecal fistula persisted and remained open all summer. Bowels continued to move three or four times daily. In October, 1919, he was again operated upon by Dr. Wilensky. The fistula was closed. For the next year the bowels moved two or three times daily. Occasionally he would get attacks of diarrhea with more frequent movements, but without cramps. Such attacks usually lasted all night. In December, 1920, he suffered from an attack of acute intestinal obstruction. Resection of about a foot of ileum; the boy made a good recovery. The blood Wassermann was negative.



After this operation the patient felt well. His bowels moved two or three times daily, once or twice in the morning and once or twice after supper. There are no cramps with these movements. In January, 1922, he had an attack of six hours duration of abdominal pain, generalized and severe, with complete obstruction of the bowels. No vomiting, some fever. General impression, acute intestinal obstruction. Immediate laparotomy; large exudate of yellowish purulent material gathered for greater part on right side and under cover of great omentum and transverse colon; bowels distended; bowel well injected but not thickened and covered with fibrin in places. No local lesion was discovered to account for the peritonitis. Drainage was provided and the abdominal wall closed. A culture of the pus showed no pneumococci. The boy made an uneventful recovery.



FIG. 1.—Ascending colon, Case I, showing tumor constricting gut.

*Macroscopical Description. Colonic Specimen* (Fig. 1). The specimen consists of a piece of large gut 14 cm. long; the lumen of the middle half for a distance of 9 cm. is extremely constricted so that it is impossible for even the small finger to pass through. On opening the gut this constriction is found to be due to an extensive infiltrating swelling which begins imperceptibly at the proximal portion of the intestine so that the upper entrance to the structure is funnel shaped. The swelling becomes gradually thicker as one proceeds downward where it ends almost abruptly by a much thickened smooth and rounded ridge. The mucosa at each end appears perfectly normal; as it approached the thickening the folds become larger and smoother; on the summit the mucosa is almost per-

fectly smooth. The gut surrounding the strictured portion is tremendously thickened. On section through this portion the thickening involves all the layers: the mucosa, musculature and the mesenteric fat. The thickening is dense, hard and white. The external surface is comparatively smooth where it has been peeled away from the surrounding connective tissue. There are a few hemorrhages into the fatty layer.

*Microscopical Examination.* The mucosa shows a classical membranous inflammation. The superficial mucosa is congested and covered by a layer of varying thickness of fresh fibrin which springs from numerous crypts in the mucosa. In extensive areas the mucosa has been destroyed revealing ulcers covered by fresh fibrin beneath which the submucosal lymphatic tissue has been converted into frank granulation tissue. With the low power the entire thickness of the gut appears densely infiltrated. The cells are either heaped together in circumscribed clumps resembling the normal lymphoid structures of the intestine or scattered in lesser or greater densities throughout all the tissues. The clumps as well as the scattered infiltrations lie within the muscular zones causing extensive deformity of the muscle bundles. They are abundant in the fatty and connective tissues external to the muscular coat as well. With the higher power the infiltrating cells are those of the round- or plasma-cell type. In the more superficial tissues polymorphonuclear leukocytes are abundant, due to the contiguous acute membranous inflammation, but in the deeper tissues these are practically absent. A noteworthy finding is the presence of abundant giant cells. These are usually present within the solid lymphoid gland-like clumps of round cells described above. In some sections they are more abundant than in others and they are present in the deeper portion of the specimen as well as in the superficial. The giant cells are usually very large, oval or irregular in shape and connected with their immediate environment by numerous "pseudopodia." The giant cells contain numerous nuclei irregularly distributed. A rather strange finding is the presence of giant cells in what seems an apparently normal lymph follicle in a portion of contiguous colon that is otherwise entirely normal.

The vessels aside from containing abundant polymorphonuclear leukocytes in the superficial portions, show no change. Sections stained for tubercle bacilli and by Levaditi are negative.

*Macroscopical Appearance of Resected Small Intestine.* (Fig. 2) Specimen consists of a portion of small intestine about 8 inches long; with the exception of a small portion at each end, the gut is extremely thickened and enlarged. The peritoneal surface is much congested and is covered with fresh fibrin. Cross-section shows an immense thickening of all the coats of the gut so that the lumen is merely a bare slit. The infiltration involves the adjacent mesentery which averages 1 cm. in thickness; the villi are much

thickened and in consequence appear much wider and rounded than normal. The mucosa is deeply congested and the lumen contains a moderate quantity of fresh fibrin which covers the surface of the mucosa. Removal of the fibrin reveals numerous superficial flat ulcerations. The transition of the thickened portion of intestine into the normal is gradual.

*Microscopical Examination.* The microscopical appearance is practically identical with that of the preceding with one important and notable exception, namely, the presence of a far greater number of giant cells, the majority of which contain a peculiar foreign body. The giant cells are so abundant that on the average three or four are in every low power field. Many are still within the clumps of lymphoid-like tissues, but they now show an extremely



FIG. 2.—Cross-section of the small intestine, Case I, showing almost obliteration of the lumen by the granulomatous tissue.

irregular distribution. They lie imbedded within the muscular fibers surrounded with a sparse collection of round cells. Many are even in the subperitoneal connective tissue coat or in the mesenteric attachment. The giant cells (Fig. 3) are extremely irregular in size, usually round or oval in contour and have a scalloped border from which numerous pseudopodia connect it with the surrounding round cells. The nuclei are abundant and stain deeply. The nature of the containing foreign body cannot be distinctly made out, because morphologically the thing, even under oil immersion, has no definite structure or outline. As a rule it is round, sometimes oval, sometimes biscuit-shaped. It appears highly refractile and stains either not at all or pale with hematoxylin. Sometimes it appears coarsely lamellated; at others it consists of irregularly shaped refractile masses; sometimes a

giant cell, may enclose a simple faintly staining striated curved rod. In one or two the foreign body appears to have a radial arrangement. Whatever the masses may prove to be there is no question but that their structure is so dense as to have been injured by the microtome, because in the vast majority these foreign bodies apparently have been disrupted. It is for this reason that they lack definite structure. Sections stained for tubercle bacilli and by Levaditi are negative.

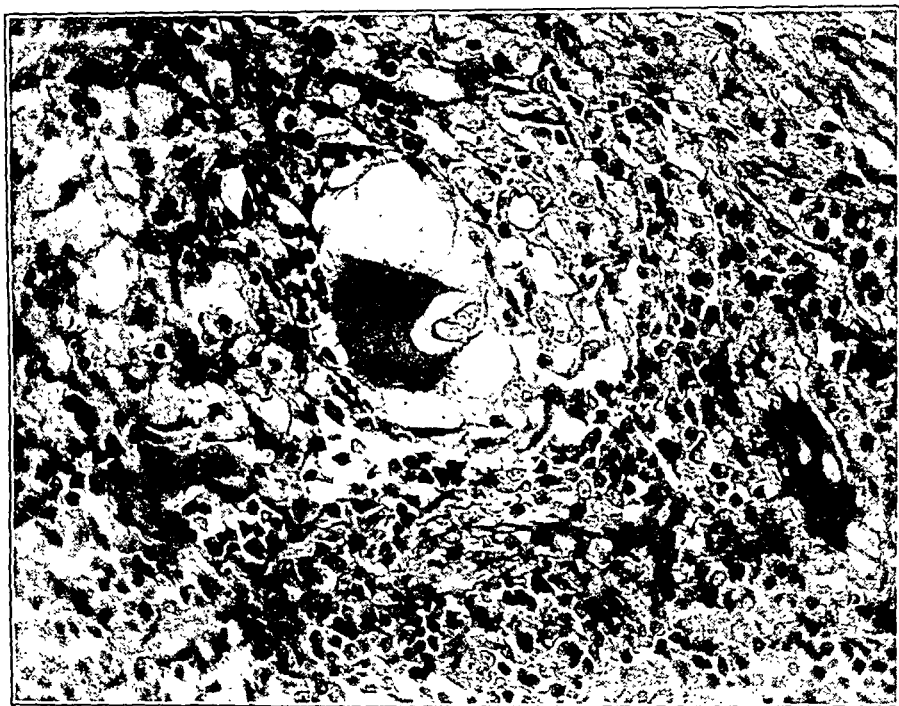


FIG. 3.—High power of a giant cell, showing foreign body.

*Summary.* A man, aged twenty-three years, suffered from a diarrhea of a year's standing which responds to treatment. He is operated upon for an acute suppurative appendicitis. Six months later a mass in the right iliac fossa appears which is resected and proves to be a granuloma. He remains practically well for two years when an attack of acute intestinal obstruction occurs. At operation about a foot of ileum is resected. The gut is almost completely obstructed by a granulomatous growth extending throughout the length of the gut. Microscopically this growth is characterized by the presence of numerous giant cells surrounding foreign bodies of unknown nature. A year later an acute suppurative peritonitis occurs the origin of which could not be determined at operation. The patient at present suffers from a mild diarrhea, but is otherwise well. Every clinical and microscopical evidence of tuberculosis or syphilis is lacking.

CASE II. (Obtained through the kindness of Dr. Seward Erdman.)—J. K., Russian, aged thirty-three years, operated upon at New York Hospital by Dr. Erdman in April, 1920, when he performed a resection of the cecum and ascending colon with lateral ileo-colic anastomosis. Eight days previous to admission he had suffered from pain in the right lower quadrant with vomiting and constipation. He denied having had any such symptoms previously. His appendix has been removed in the course of an



FIG. 4.—Ascending colon from Case II, showing stricture of the lumen by the granulomatous infiltration.

operation for right inguinal hernia in October, 1917, at the New York Hospital, at which time the operator (Dr. Viotor) remarked that the appendix was delivered into the wound with some difficulty and with some trauma to the cecum. The appendix did not appear to be diseased and it certainly was not indurated enough to interfere with the usual technic of invagination of the stump. In April, 1921, Dr. Erdman examined the patient and no masses in the abdomen were palpable. The patient said he felt perfectly well, had gained 20 pounds and was not suffering from any gastric or intestinal symptoms.

*Macroscopical Description.* (Fig. 4.) Specimen consists of a portion of large intestine 8.5 inches long. The opened bowel

reveals a raised tumor-like projection extending longitudinally at about its middle portion. The mass is situated on the posterior aspect, and measures 2 inches in the vertical diameter and 1.5 inches transversely at its widest portion and is three-quarters of an inch thick at its highest elevation. The mass is egg-shaped. The lower margin is thickened, curved with its convexity downward and overhanging. From here the mass narrows slowly as it courses upward and merges imperceptibly into the mucosa. Laterally the tumor overhangs the adjacent mucosa at its lower portion; above it merges gradually into the surface of the bowel. At about its middle, there is a flat ulceration with a slightly



FIG. 5.—High-power section of colon, Case II, showing nature of the granulomatous infiltration.

roughened base, somewhat circular and measuring about 2 cm. in diameter. The surface otherwise is uneven, but the usual Kerckring folds are absent. Section through the mass shows a dense infiltration of all the coats of the intestine for a considerable distance beyond the confines of the mass.

*Microscopical Examination.* (Fig. 5.) Incidentally this section is representative of all the cases we present. The mucosa appears everywhere intact except at the site of the ulceration. Morphologically no abnormality is visible. The remaining coats of the gut are densely infiltrated with cells mostly of the round and plasma type. These cells are heaped together in dense but not

sharply circumscribed areas so that even grossly the cut section appears as though studded with tubercles. But there is a very great diffuse infiltration in all the tissues especially in the muscular layers so that the muscle bundles are separated, disorganized and deformed. The submucosa and subperitoneal connective tissue coats are much thickened due to an obvious fibroblastic transformation. These layers have all the appearance of young fibrous tissue. The lymphoid structures are intact and reveal nothing abnormal. The bloodvessels are numerous and show some thickening of the media. No giant cells are at all visible. In one section taken from the ulcerated area there is a circumscribed and apparently extensive infiltration with polymorphonuclear cells in the submucosa forming a small abscess. Lymph nodes removed from the mesentery are fairly large and are normal. Sections stained for tubercle bacilli and *Spirocheta pallida* are negative.

*Summary.* A man, aged thirty-three years, is operated upon for an inguinal hernia at which time an appendectomy is performed. Two and a half years later acute symptoms resembling those of an attack of appendicitis arise. A large mass in the ascending colon is found which proves on microscopical examination to be a simple chronic granuloma. The patient up to last reports is entirely well.

CASE III.—L. D., tool maker. Presbyterian Hospital (42738) (Path. No. 26199), admitted July 23, 1919. Five days previously had abdominal pain and vomiting. Appendectomy with drainage by Dr. Langworthy. Toward the end of convalescence the patient complained of pain in right upper quadrant and back. This persisted and is getting worse. Fever of 101° F. since onset.

*Physical Examination.* There is dulness in right upper quadrant extending to midline. Tenderness in this region extends back to spine. Recent healed appendectomy scar is visible. Stool and Wassermann were negative as well as the urine. No fever.

*Readmission.* April 24, 1921. Three weeks' complaint of general malaise, chilly sensation, pains in left lumbar region. The patient was told he had "nephritis;" later the physician diagnosed abscess around left kidney. Bowels were costive.

*Physical Examination.* In the left flank a mass is felt on bimanual examination, tender, smooth, firm, which can be pushed forward and backwards. No fever.

*Diagnosis.* Perinephritic abscess. Roentgen-ray shows a slightly enlarged left kidney, but no tumor of colon.

*Operation.* May 14, 1921, Dr. Auchincloss. Colectomy for mass just below splenic flexure.

*Macroscopical Description.* (Fig. 6.) The specimen is a segment of larger intestine, 21 cm. long. It is curved, forming the letter C about a central mass of tissue to which it is densely adherent.

This mass is composed of a rolled-up bunch of fat, the center of which is filled with innumerable whitish or reddish-yellow amorphous masses which suggest caseation but are not so soft. The colon is contracted, thick walled and contains fecal material. On section the colon appears normal, except in the distal edge of one segment of the gut where the tumor has encroached to the very edge of the mucosa but apparently has not broken through. The tumor at this point has been much narrowed.

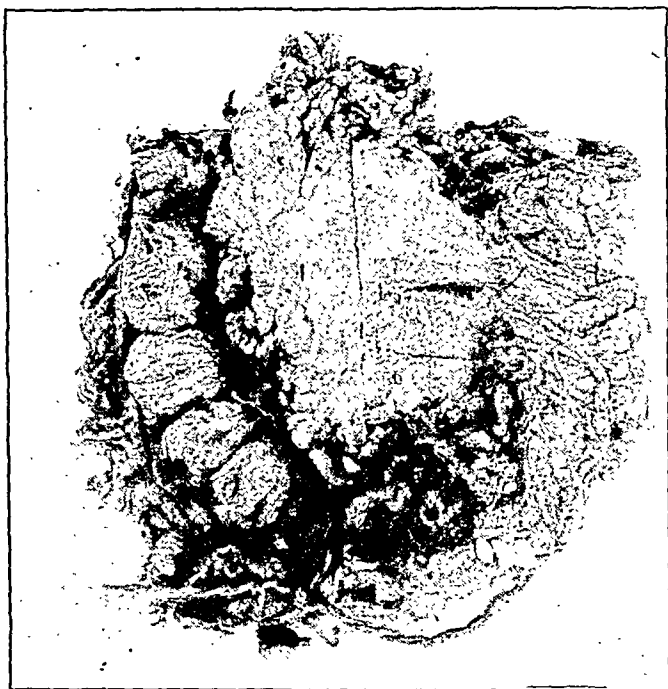


FIG. 6.—Splenic flexure, Case III, showing granuloma of the mesentery infiltrating intestinal wall.

*Microscopical Examination.* Sections of the mesenteric mass shows a fibroblastic tissue containing many capillaries and densely infiltrated with round and plasma cells and leukocytes. The round cells predominate. In some places the cells are closely massed together which probably accounted for the yellow masses described in the gross. There is little actual necrosis of tissue. Section of one of the lymph glands on the outside of the mass shows a wide dilatation of the lymph sinuses with reticulum in which a few mononuclear cells are caught. Gram stain is negative. Section of the wall of the larger intestine shows a thin but intact mucosa with normal appearing glands and a slightly edematous stroma infiltrated with a few leukocytes and plasma cells. The muscular coat is edematous and densely infiltrated in many places with round cells. The submucosa is considerably thickened, quite vascular



and infiltrated with many polymorphonuclear leukocytes and a few round cells. Serosa covered with thin layer of fibrin.

*Diagnosis.* Chronic colitis, chronic mesenteric lymphadenitis. A blood Wassermann taken after discharge was negative. A fistula resulted which was closed by Dr. Auchincloss. The patient reported in November, 1921, as being perfectly well.

*Summary.* A man, aged forty-four years, is operated upon for an acute suppurative appendicitis. Appendectomy is performed. After the operation symptoms and signs suggestive of an inflammation in the right side of the abdomen appear which slowly subside. Nearly two years later he presents himself with a mass in the left kidney region which proves upon operation to be, a granulomatous mass in the splenic flexure of the colon, the main bulk being in the mesentery but involving the walls of the gut and apparently not breaking into the mucosa. Microscopical examination reveals no evidences of tuberculosis, syphilis or lymphogranulomatosis. The patient up to last reports remains well.

CASE IV.—L. O., aged forty-four years, admitted to Presbyterian Hospital, December 26, 1918. (Presbyterian Hospital 40305 Path. Lab. 22256.) Three weeks ago she was seized with abdominal pains, cramp-like; vomited at onset. There was swelling of the abdomen, most marked in right upper quadrant, which went down considerably after a copious urination. Has had no severe pain since onset.

*Physical Examination.* In the right upper quadrant of the abdomen is a tender mass, extending to the upper epigastric region. It is round, smooth, somewhat movable and seems to descend on inspiration. This mass seems to be the lower pole of the kidney. Otherwise examination is negative. Wassermann is negative. Feces show no blood. Roentgen-ray shows a filling defect in the ascending colon just below the hepatic flexure.

*Operation.* January 18, 1919, Dr. Whipple. Colectomy and ileocolostomy. *Macroscopical Description.* The specimen consists of a cecum, appendix and a short portion of the ileum and ascending colon. The serosa of the cecum is smooth, the vessels are slightly dilated. There is a firm irregular nodular mass on the lateral aspect of the ascending colon, 13 cm. from the fundus of the cecum. The appendix is small, 3 by 0.3 cm. The lumen is obliterated. The cecum on section contains feces. The walls appear normal in thickness. The wall of the ascending colon is moderately thickened and the site of the dense mass described above. At one point there is a small nodule 1 by 3 cm. projecting into the lumen of the gut. Section through the larger mass shows a relatively dense tissue having a mottled yellow and white appearance. The gut wall is thickened at this point and the mass is adherent to it. Section through the small mass projecting into the lumen shows it to be

closely connected with the main tumor mass at a point in which the yellow substance described above is found in small areas in the gut wall extending as far as the mucosa.

*Microscopical Description.* All the coats of the intestine are densely infiltrated by a fibroblastic process which varies from a cellular and apparently fresh granulomatous tissue, with many newly-formed blood spaces to a comparatively dense fibrous structure. This new tissue is especially prominent in the submucosa and infiltrates the muscle to such an extent as to cause extensive separation and distortion of the bundles. The predominant cells are of the round type. These cells are heaped together in dense masses in many areas. There is no necrosis and no giant cells are found. The appendix shows complete obliteration of the lumen by fibrous tissue and extensive fibrosis of the muscular coats. The serosa is thickened and infiltrated with round and polymorphonuclear cells.

*Diagnosis.* Chronic colitis, chronic appendicitis.

Patient recovered and was discharged February 8, 1919. On July 17, 1919 she reported herself well.

*Summary.* A woman, aged forty-four years, is seized with sudden cramp-like pains in the right side of the abdomen. Upon admission three weeks later a large mass is noted in the right iliac fossa which proves upon roentgen-ray examination to involve the ascending colon. At operation, the mass is resected. Microscopically it proves to be a simple granuloma. The appendix reveals chronic inflammation. No microscopical evidences of tuberculosis, syphilis or lymphogranulomatosis are noted. Up to last reports the patient remains well.

According to criteria of pathology these 4 cases may be classified as "granulomata of non-specific morphology." All evidences of tuberculosis, syphilis, lymphogranulomatosis (Hodgkin's disease) or new growth are lacking.

*Gross Characteristics.* All 4 specimens with the exceptions of the small intestine (Case I) resemble one another closely. There is a firm dense uncircumscribed tumor involving all the coats of the large intestine causing stricture of the lumen. There is ulceration in all but 1 (Case III). The ulceration is comparatively superficial and does not penetrate beneath the mucosa. In 3 cases the ascending colon is involved, in the fourth the splenic flexure. The second specimen from the first case is the only one in which the small intestine is involved. It also involved all the coats of the intestine and the encroachment into the mucosa was so great as to cause almost complete obliteration of the lumen. Involving, as it does, almost a complete foot of the small intestine, the lesion, as far as we have been able to investigate, is unique. The infiltration was most prominent on the mucosal aspect of the

intestine in 3 cases. In the fourth, the main bulk of the tumor projected into the mesentery.

**Microscopical Characteristics.** The 5 specimens, again with the exception of the small intestine, reveal a uniformity in microscopical morphology. There is an extensive infiltration of all the coats with cells of the round- or plasma-cell type. It is hard to determine in which layer the infiltration is greatest, but to us the submucous layer seems most extensively involved. There is a widespread fibroblastic transformation varying from a comparatively richly cellular tissue to firm dense fibrous scar. The number of polymorphonuclear leukocytes in our specimens varies considerably. In those with ulceration they are numerous in the neighborhood of the ulcer. In the second case they are congregated in such abundance in the submucosa in one area as to justify the term abscess. In the remaining portions of our specimen these cells are only sparsely scattered. New bloodvessel formation is prominent in all specimens.

Giant cells are absent in all cases except the first. In both specimens from this case their distribution and morphology is so remarkable as to merit detailed description. In the first specimen removed from the ascending colon, the giant cells while easily found are not especially numerous, and are distributed equally throughout all coats of the intestine. They are large, have irregular dentated outlines and contain numerous nuclei irregularly distributed. They have none of the characteristics of either the giant cells of the Langhans type or the Reed-Sternberg type. A careful search reveals no evidence of foreign body in or contiguous to these cells. In the specimen of the small intestine removed from this patient, the giant cells are extremely numerous, three or four being present in almost every field. While morphologically they resemble the giant cells found in the colonic specimen, in these a foreign body is found within the majority of these cells. These foreign bodies have a varying morphology, usually they are round, oval or biscuit in shape, with a granular or highly refractile content and a dense lamellated capsule. What these foreign bodies are we have not been able to determine. They do not even afford the possibility of a guess.

In none of our specimens is there the slightest evidence of necrosis or caseation.

In Cases I and II, sections were stained for tubercle bacilli and the *Spirocheta pallida* but were not found. Bacterial stains on Cases III and IV were not made.

Sections of the mesenteric lymphatic glands reveal nothing noteworthy.

**Discussion.** It is a remarkable fact that non-specific inflammatory tumors of the intestine were, with few exceptions, not described until 1908. Practically the entire literature upon the

subject dates from the publication of Braun<sup>1</sup> in that year, and it is his report that has stimulated subsequent studies. It is true that in 1898, Graeser, in a classical paper, called attention to inflammatory processes in the sigmoid flexure arising from acquired diverticula, but such lesions, although morphologically similar to those in which we are interested, do not enter into our discussion. The reason of this curious absence of comment is the fact, as we shall discuss more fully in a subsequent part of this paper, that these cases were regarded as instances of "hyperplastic tuberculosis of the intestine."

Braun's case was that of a woman, aged forty-three years, who presented a tumor on the left side of the abdomen of eight weeks' duration. The bowels were irregular, often tinged with blood. Diagnosis, carcinoma. At operation a mass in the sigmoid flexure was found which involved mostly the mesenteric aspect. The mucosa covering the growth was normal. Microscopically the tumor consisted of a poorly cellular connective tissue infiltration of the meso-sigmoid which extended partly into the muscularis and the submucosa. In one portion there was a broad streak of round celled infiltration which penetrated to the mucosa.

The number of case reports since Braun's publication has been large and year by year shows a progressive increase, so that it is safe to say the malady is not at all a rare one.

We do not propose to submit a complete digest of all the literature pertaining to the subject. Those interested may refer to the fairly complete and most recent studies of Tietze<sup>2</sup> and Körte.<sup>3</sup> We shall merely content ourselves with giving a summary of the pathology, some of clinical aspects and the etiology.

**PATHOLOGY.** Each of our cases exemplifies in one way or another the characteristics common to this lesion. There is a tumor of greater or lesser size which may involve any portion of the colon. Even in the sigmoid many such lesions are described without in anyway being associated with a diverticulitis. The inflammatory process usually involves all the coats of the intestine. Sometimes the proliferation is most prominent in the inner coats forming smaller or larger tumors which narrow the lumen of the gut. Less frequently the proliferation seems to begin in the mesenteric attachment forming tumors sometimes even as large as a child's head, which involve the walls of the gut by continuity and cause stricture of the lumen. In the former, there is ulceration of the mucosa, which, as a rule, is superficial and not extensive; in the latter the mucosa appears perfectly normal or slightly thickened. Adhesions to surrounding structures and to the abdominal wall are common. In a few instances, the induration has extended to the ileo-cecal valve causing narrowing of this structure. Abscess formation is rare, and when present is slight as in one of our cases.

MICROSCOPICALLY. These tumors reveal typical granulomatous changes in various stages of senescence and the descriptions we have submitted in reporting our cases (excepting Case I which is almost unique) cover the ground quite fully. There is never the slightest evidence of tuberculosis, syphilis, lymphogranulomatosis or new growth.

The remarkable resemblance of some of the cases which we report to hyperplastic tuberculosis of the intestine led us to a study of the literature of this malady in order to check up our findings. We have arrived at the conclusion that undoubtedly many if not a majority of so-called "hyperplastic tuberculosis of the colon" are really simple granulomata. Indeed the majority of authors of comprehensive papers on "hyperplastic tuberculosis of the intestine" describe lesions that are identical in every way to those which we have reported. For instance Lartigau<sup>4</sup> says, "More often the tubercles are mere aggregations of lymphoid cells in which one or more giant cells are seen. Epithelioid cells are usually absent. Many show little tendency to necrotic change; a distinct tendency to fibrous transformation is apparent. *The typical histological features of tubercle bacilli are often absent*; in lieu thereof there may exist a diffuse embryonal cell differentiation, at times capable of simulating sarcoma." Ignard<sup>5</sup> says, "In many cases of hyperplastic tuberculosis of the intestine, no tubercles, giant cells or bacilli are found. The lesion is constituted of a mixture of variable proportions of tuberculous and inflammatory elements. *In certain cases, the last only exist*. Nevertheless, these inflammatory tumors should be classified among the tuberculous." Itie<sup>6</sup> says, "The tuberculous elements are relatively rare. More often you find simple follicles with two or three giant cells. The zone of epithelioid cells is wanting, and only a crown of round cells surrounding a giant cell is found." Pilliet and Hartman<sup>7</sup> say that "Hyperplastic intestinal tuberculosis differs from the common tubercle. The tuberculous follicles are relatively rare; the embryonic infiltration on the other hand is more marked." Weiting<sup>8</sup> after calling attention to the fact, "That tuberculosis may cause an immense amount of connective tissue infiltration without any tendency to break down," remarks in a late portion of his paper, "that a diagnosis of tuberculosis must be excluded unless tubercles with giant cells are present." Shiota<sup>9</sup> who describes 24 cases of so-called hyperplastic tuberculosis remarks, "That it is common not to be able to differentiate the lesion from an inflammatory hyperplasia." Ipsen<sup>10</sup> says, "That tuberculosis may be present even though the characteristic histological reaction is absent, and that the diagnosis can only be confirmed by animal inoculation." Incidentally, as regards intestinal tuberculosis, we have been unable to find in the literature that this procedure has

been performed. He regards "a late invasion by the organism as a possible explanation for the absence of the characteristic histological characters." Doubt seems to have crept into the mind of but one observer, Richter.<sup>11</sup> He believes that hyperplastic tuberculosis is really a non-specific inflammation of the cecum and that the tuberculosis is only an accidental infection and complication, the result of swallowing tubercle bacilli either from a pulmonary focus or in milk.

It does not require much reading of studies of intestinal tuberculosis to discover that observers have copied each other's discussions closely. For instance, nearly all try to account for the non-tuberculous characteristics of their lesions by likening them to lupus. It remained for Richter to disclose the fallacy of this assumption. Furthermore, all comment on the sparseness, or what is more significant, the absence of tubercle bacilli in such tissues, although only very few mention any attempts at finding them in the lesions they report. At all events, the scarcity of bacilli is supposed to account for the absence of the typical histological characters of tuberculosis in these lesions, but on what grounds we do not know. Tubercle bacilli are scarce in many frankly tuberculous lesions, but nevertheless, the lesions are unmistakable. The absence of bacilli in the lesions they describe is certainly significant, but this seems to have escaped notice.

We believe, therefore, with more rigid methods of histological study, the number of true hyperplastic tuberculosis of the intestine will diminish appreciably and that in the future fewer will be reported than heretofore.

The criticism we have submitted also accounts in a large measure for the comparative absence of reports of non-specific granulomata of the intestine up to the year of Braun's publication.

**ETIOLOGY AND PATHOGENESIS.** In the vast majority of the reported cases the etiology was unknown. A curious feature in all 4 cases which we report is the history of a previous appendicitis or appendectomy. In 2 cases (I and III) a definite acute suppurative appendicitis preceded the onset of signs six months and two years respectively. In Case II an appendectomy in the course of herniotomy was performed three years previously. (Whether the appendix was diseased or not can no longer be determined.) In Case IV the history suggested an acute appendicitis three weeks previous to the onset and pathological examination of the appendix revealed a completely obliterated organ.

The relationship of inflammatory lesions of the colon to appendicitis is repeatedly broached in reported studies. (De Ruyter,<sup>12</sup> Gangitano,<sup>13</sup> Læwen,<sup>14</sup> Gato,<sup>15</sup> Teitze,<sup>2</sup> Körte.<sup>3</sup>) In most of these reports however, the inflammatory process is continuous with that of the appendix and involves only the contiguous portion of the

cecum. In other instances mere coproliths are present or old obliterations at the tip. Despite the frequent associations of inflammatory lesions in the colon and appendicitis, we are forced to the conclusion, taking into consideration all possible genetic factors, that this relationship is entirely coincidental. We cannot conceive how a chronic granuloma in the colon can arise at a distance from an inflamed appendix removed six months or two years previously or an appendectomy performed three years before the onset of signs. Even if such a late infection were possible, it could only arise by way of the lymphatics, and while it is true according to Bartels<sup>16</sup> that the lymphatics of the appendix and cecum anastomose, the current is in the reversed direction. To assume that an infection occurs in the retrograde direction would be stretching possibilities unduly. Another possibility is that the presence of a dormant infection in the gut contributed to an infection of the appendix. There is little question, judging from the morphological characters, that the granuloma was present in the gut long before clinical manifestations became apparent and it is conceivable that such a mass, probably already ulcerated, would render an infection of the appendix more liable. In this connection it is interesting to note that a primary typhlitis of the cecum, a lesion resembling those which we describe very closely has been reported occasionally, in many instances such a lesion being regarded as the course of a subsequent appendicitis. For many years the occurrence of a primary typhilitis was doubted but it unquestionably occurs. Haim<sup>17</sup> reports many such.

There are a number of case reports of granuloma of the colon in which foreign bodies were the direct cause. Jaffe<sup>18</sup> found a tumor the size of a fist involving the colon in the center of which a small piece of bone was found. Schreiber<sup>19</sup> reports a large ulcerating granuloma of the ileo-cecal region in which many cherry and plum pits were present. Marion<sup>20</sup> reports a piece of bone in a large granuloma of the ascending colon adherent to and involving the rectus muscle. Tietze<sup>2</sup> reports a granuloma in the cecum following an operation for acute appendicitis. In the center of the granuloma the silk thread employed in ligating the appendix was found. Wölfler and Lieblein<sup>21</sup> in their comprehensive monograph on "foreign bodies in the intestine" remark on the frequency of lodgement of such bodies in the cecum where they give rise to large inflammatory thickening with adhesions and occasionally to perforation with chronic abscess formation.

The only specimen in our series in which a foreign body was present is Case I in which microscopical foreign bodies of unknown structure were found enclosed within giant cells. What the nature of these structures are is unknown to us. These foreign bodies we believe penetrated into the wall of the gut through previous

ulceration consequent to colitis. No foreign bodies were found in the other specimens, either on section or by roentgen-ray.

A colitis or dysentery has been reported as preceding the onset of these granulomata by numerous writers, (Monsarrat<sup>22</sup>, Rosenheim,<sup>23</sup> Strauss,<sup>24</sup> Birt and Fisher,<sup>25</sup> Koch,<sup>26</sup> Gato<sup>15</sup> and Tietze<sup>2</sup>). In our first case a colitis was probably the origin of the granuloma, if a long standing diarrhea with blood and mucus in the stool is at all diagnostic of a colitis. Tietze reports a case of inflammatory tumor of the sigmoid flexure following irrigation of the lower bowel with a strong silver nitrate solution.

The derivation of granulomata from diverticulitis of the sigmoid is well known. This malady, however does not enter into our discussion.

In the vast majority of instances the cause of the granuloma is unknown. We must presume that there is some infectious agent of low grade violence which enters through the mucosa. Distribution of the infection by lymphatics is in most instances highly probable. The lesions remind one strongly of the granulomata described by Braun<sup>27</sup> and others which occur in the omentum following ligation and resection of this structure in herniotomies and which are due to infections from silk or catgut. Rarely, these granulomata arise from infections in the stomach, Fallopian tubes or ovaries. They also resemble the inflammatory tumors of the abdominal wall described by Schloffer,<sup>28</sup> arising after operations for hernia, in which silk stitches are occasionally found imbedded within the tumor.

**CLINICAL CONSIDERATIONS.** A survey of our report readily leads to the deduction that the lesion we report offers no characteristic clinical concept: the etiology, symptoms and signs are too protean and indefinable. Evidence of a stenosis of the gut and the presence of a mass in the abdomen are by all odds the most constant phenomena. The most prevalent diagnoses have been malignant growth, hyperplastic tuberculosis and appendicitis and most observers agree that a correct preoperative diagnosis is impossible. The most interesting and diagnostic characteristic in connection with these granulomata of the intestine is their disappearance after a simple sidetracking operation. Moynihan<sup>29</sup> and Robson<sup>30</sup> report such instances. Obviously the presence of a tumor of this variety has a profound bearing on prognosis.

**Conclusions.** 1. Four cases of non-specific granulomata of the intestine are described. All involved the colon, 1 involved both colon and small intestine.

2. The histological characteristics are those of a simple granuloma. No evidences of tuberculosis, syphilis or lymphogranulomatosis are present.

3. The granulomata may involve any portion of the colon.



The infiltration of the wall may be more prominent on the mucosal or the mesenteric aspect. In both instances the lumen is narrowed. Ulcerations, which are usually superficial, may be present; exceptionally, abscess formation.

4. The cause most often is unknown. In a few cases foreign bodies and a colitis have been reported. Despite the association of the lesion with a previous appendiceal involvement we do not believe that appendicitis has any direct causal relationship to the malady.

5. Clinically, these cases present signs of constriction of the intestinal lumen and a mass in some portion of the colon. Thus far, they are not diagnosticable before operation and have usually been mistaken for carcinoma and tuberculosis of the intestine. Not infrequently these tumors disappear after simple sidetracking of the intestine. The prognosis is excellent.†

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† We wish to express our profound thanks to Drs. Seward Erdman, W. C. Clarke and P. Stout for the privilege of reporting their cases.

## THE ROLE OF SPASTICITY IN DISEASES OF THE DIGESTIVE TRACT.\*

### A CASE OF VISCERAL TETANY, CAUSING ACUTE CHOLANGITIS AND PANCREATITIS.

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It is the object of this paper to contribute to a better understanding of the role which spasticity may play in diseases of the digestive tract.

The knowledge of abdominal spasticity is not new. The writings of older clinicians show that they were familiar with the phenomenon. Roentgenology however, demonstrated its great frequency and taught us to differentiate more sharply its various forms and types and their relation to tonus, peristalsis and segmentation (hypermotility, hyperperistalsis, tonic and tetanic contractions). Granted that the appearance of spasticity has generally been recognized, its interpretation and valuation is often far from satisfactory.

Its frequent occurrence with local conditions, such as traumatic lesions, stones, acute inflammations, ulcerations and cancer, led to the more common explanation of spasticity as a manifestation of localized character, a plausible explanation on account of the automatic activity of the ganglia implanted in the digestive tube. And yet operative, as well as postmortem inspection, found the lesion often at a different spot than the location of the spasm would indicate. Ulcer or cancer at the cardia with spastic obstruction in the upper part of the esophagus; ulcer or cancer at the smaller curvature with pronounced spasm of the uninvolved cardia; gall stones and cholecystitis associated with true gastrospasm or with tonic contractions in the colon and sigmoid. The spasm in parts distant from the lesion is produced reflexly over the paths of the vegetative nerves which regulate the coöperation of the different sections of the digestive tube. Reflex spasm may also originate from organic lesions outside the alimentary canal, from diseases in the central nervous system, the pelvic and other organs. These two types, local and reflex spasm, will not be further discussed here since they predominate in the interpretation of spasticity at present. I rather intend to emphasize a fact too often overlooked, that spasticity, eventually of a very high degree, may, as the result of systemic derangements occur without the presence of a local lesion.

\* Read at the Twenty-fifth Annual Meeting of the American Gastroenterological Association at Washington, D. C., May 1, 1922.

**AUTONOMOUS SPASTICITY.** The conception has been entertained long ago that spasticity may present itself as part manifestation of conditions which we are still accustomed to class as general neuroses.

In his classic essay on "Peristaltic Unrest" Kussmaul<sup>1</sup> attributed the painful and visible hyperperistalsis of the stomach and the bowels, to a highly increased irritability of the peristaltic nerves in neurotic individuals, at the same time stating with regret that the term motor neurosis did not convey much meaning. Under his influence Fleiner<sup>2</sup> defined spastic constipation.

The modern study of the working of the vegetative nerves, greatly stimulated since the description of vagotomy by Eppinger and Hess,<sup>3</sup> has considerably advanced the understanding of spasticity of systemic origin.

We have learned that normal activity of the digestive apparatus requires a harmonious interplay of the vagus and the sympathetic and that it depends on a maintenance of steady tonus in the two systems. However, the habitual tonus of the vegetative nerves varies greatly as to degree in different individuals, and even in the same person it varies at different times according to his constitutional make-up. Constitution has been aptly defined as a person's characteristic way of reacting to internal and external stimuli. Coined on this basis, the term "spastic constitution" is suggestive. Such definitions make it easier to comprehend that the same type of local lesion may provoke frequent and severe spasm in one person, and rarer and milder spasm in another; and further, that a local lesion may exist without causing spasm, that for instance, stones in a gall-bladder may remain dormant, often for a long period of time, until something occurs in the system which provokes spasm in the biliary ducts and with it "an attack." Even the structural narrowing caused by cancer often becomes evident only at a time when spasm is superimposed and produces the symptom-complex of obstruction. Persons with habitually high irritability of the vegetative nerves seem to be disposed to a further increase of tonicity by anything affecting their physical and mental balance, foremost of all by fatigue after physical, mental, or emotional taxation.

Once we have reached this viewpoint, the association of local lesions with spasticity may appear in a different light. While in certain conditions the local lesion must be held chiefly responsible for bringing on the spasm, for other conditions the question may well be asked whether the spasm is not primarily the result of systemic influences, and instead of being an effect, is not, in fact, a causative element in the development of the lesion.

<sup>1</sup> Samml. klin. Vortr., 1880, No. 181, p. 1638.

<sup>2</sup> Berl. klin. Wchnschr., 1893, 30, 60.

<sup>3</sup> Die Vagotonie, Berlin, 1910.

SPASTICITY AS A CAUSATIVE FACTOR. The valuation of spasticity as a causative factor has been extensively dwelt upon in the discussion on the pathogenesis of peptic ulcer. Experimental investigators, pathologists and clinicians join in the contention that the primary lesion, that is, the miliary ecchymoses, are caused by spasm of the muscularis mucosæ which constricts the small end-arteries and leads to ischemia and extravasation. When a strong peptic secretion is present, which like the muscular spasm is the result of excessive vagus tone, the poorly nourished part of the mucosa in the area of ecchymoses is digested, and we have an erosion. The development of an erosion into an ulcer and its further growth are possible, however, only when there is more than temporary overirritation of the vagus nerve. It requires a distinct disposition, which manifests itself by a chronic state of increased vagus tone, bringing on prolonged periods of hypersecretion and spasm not only of the muscularis mucosæ, but also of the larger muscular coat and eventually of the pyloric sphincter. The regular recurrence of spasm with each meal prevents the healing of the ulcer and makes for its chronicity. Once developed, the ulcer as a source of irritation may further increase the vagus tone thus creating a vicious circle. From the very start and through the whole course of the ulcerative process we see spasticity as an important causative element.

If we accept these views which offer a plausible theory of the mechanism in the development of certain types of peptic ulcer, we still have to answer the question: What causes the spasticity or rather the excessive vagus tone, which is at the bottom of the ulcerative process? At present the opinion prevails that it is provoked reflexly by a local lesion somewhere else in the system, especially by a diseased appendix, in short that peptic ulcer is a "secondary disease" (Rössle).<sup>4</sup> I am not ready to subscribe to this opinion, having seen too many cases where the ulcerative process recurred or even started only after the removal of the appendix, and also hesitate on account of similar experiences after other operations. On the contrary, I think clinical observations justify the contention that increased irritability of the vagus with consequent spasm may be produced directly by the action of systemic influences, (diets, etc.) metabolic disorders, autointoxication, lead or tobacco poisoning and other factors. As I pointed out four years ago,<sup>5</sup> mental and emotional overtaxation, probably by way of disordered endocrine influences, may be the principal causative element in the development of excessive vagus tone, spasticity and active periods of ulceration. Only when we realize the importance of systemic factors are we able to explain the well known periodicity of peptic ulcer. This periodicity is but a con-

<sup>4</sup> Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1912, 25, 766.

<sup>5</sup> Med. Record, 1918, 94, 324.

firmation of the axiom, that disease is not static, but a functional disorder with stages of development. The local reaction is merely a manifestation in a certain region of predisposing systemic agencies.

It is this point which I wish to stress, that spasticity resulting from systemic conditions may be a primary causative factor in peptic ulcer, and in a similar manner in other local lesions in the digestive tract. There is at present too much inclination to look for a direct causal relation between the different diseases in the stomach, intestines and gall-bladder, making one the provocative agent of the other. It is certainly true that, for instance, a diseased appendix may reflexly cause disorders of the gastric function. Such possibilities, however, are far too often generalized. It occurs to me that we may arrive at another view by investigating, whether each one of simultaneous but different local lesions met with in the same person, was not originally the outcome of a systemic disorder. This view would rather tend to coördinate them, and would minimize the influence, which after their initial development they may have had upon each other.

Without entering now upon a discussion of the nature of the underlying general condition, I repeat that spasticity caused by systemic upsets, may prove an important factor here. By approaching these problems in a changed mental attitude, clinical syndromes may assume to the observer a different significance.

Since abdominal surgery demonstrated the frequency of acute infections especially in the appendix and gall-bladder, conceptions of abdominal pathology have been strongly influenced by the picture of inflammation. The result was that not only in acute, but likewise in chronic conditions, objective as well as subjective symptoms, such as tenderness and pain, were too readily accepted as signs of inflammation. This, for instance, is clearly seen in the poorly defined syndrome of "chronic appendicitis," the diagnosis of which is principally based on the evidence of spontaneous and pressure pain in the appendicular region. The fact that in a high percentage of cases thus diagnosed as chronic appendicitis, the same spontaneous and pressure pains recur after appendectomy, proves that the pain did not originate in the removed appendix. When not caused by another local lesion or not of a purely neuralgic character, the pain in many of these cases is the result of uncomplicated enterospasm. We do well to keep in mind, that in the digestive tube, as elsewhere, spasm by itself may produce pain, eventually of severe character and of long duration.

For a while the idea of the existence of true nervous gastro-spasm and of enterospasm was actually ridiculed; it has come into its own again since the roentgen-ray visualized such spasms. It is significant that a surgeon, Liek<sup>6</sup> in Danzig, after a thorough

<sup>6</sup> Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1921, 32, 153.

study of the literature and of his own vast material, rejects the popular syndrome called chronic appendicitis. He adopts instead the term pseudo-appendicitis, attributing the pain in most of these cases to nervous enterospasm.

When the spasm is localized at the appendix, it may cause stasis, bacterial growth and inflammation. In such an event inflammation follows the spasm. Acute appendicitis is frequently preceded by attacks of "appendicular colic" without fever and without changes in the blood picture.

A similar situation may arise in the biliary tract. In a paper<sup>7</sup> read before this association nearly twenty years ago, I stated that spasm at the opening of the common duct, by causing biliary stasis, may lead to the formation of gallstones, to calculus attacks and to infections and inflammations of the bile ducts and of the gall-bladder. Gerster<sup>8</sup> independently arrived at similar conclusions in a paper in which he dealt with the causes of unsuccessful surgery in disorders of the gall ducts. And Meltzer<sup>9</sup> discussed this topic thoroughly at a symposium on diseases of the gall-bladder in 1916. That the same underlying condition of autonomous spasticity should create such entirely different products as a clean-cut peptic ulcer or a purulent inflammation is not so strange if we consider the different character of the respective secretions, especially the peculiar qualities of the gastric secretion, which not only digests poorly nourished parts of the gastroduodenal wall but also destroys bacteria.

Clinical experiences over a course of years have convinced me that spasm alone, due to systemic upsets, more frequently than is generally conceded may account for severe abdominal pain; furthermore that it may become the primary causative factor in the development of abdominal diseases including local inflammations. As an illustration I present the history of a patient, whom I had occasion to observe together with his physician (Dr. A. L. Garbat) and with other consultants.

**Case History.** L. M., male, aged fifty-five years, grew up under trying circumstances. From childhood on had to do very hard work, while for many years he was provided with poor food. At an early age dental decay set in and was neglected, so that eight years ago, all teeth had to be extracted. From early days whenever his stomach was upset frequent and long attacks of hiccoughs appeared. He always had a tendency to "indigestion" with heartburn and sour eructations. Appetite was usually good, bowels were constipated.

<sup>7</sup> Kaufmann, J.: *Am. Med.*, November, 1903, 6, 792.

<sup>8</sup> *Surg., Gynec. and Obst.*, 1912, 15, 572.

<sup>9</sup> *Tr. Am. Gastroenterol. Assn.*, 1916, p. 116; *Am. Jour. Med. Sci.*, 1917, 63, 469.

No acute attacks of pain ever occurred until the present trouble. In 1906, at the age of thirty-four, pleurisy with effusion was contracted. Was tapped twice with removal of 92 oz. of fluid. Tubercle bacilli were present in the sputum. Involvement of left upper lobe and right apex were found. After prolonged stay and treatment at Saranac, New York, was discharged with general improvement and gain of weight. No signs of an active process showed themselves until 1913, when an attack of fever and cough required his return to Saranac. After this the picture remained that of an inactive, stationary fibrosis of the left upper lobe and of the right apex. Patient returned regularly to Saranac during the summer months, and several times during the year for a few weeks, whenever he felt run down. On these occasions more cough and more sputum were noted with tubercle bacilli. During the rest of the year, the high strung, energetic, short and moderately nourished man worked steadily and over long hours as boss of a barber-shop in a big hotel, where he had "to handle from 600 to 700 customers a day."

In the summer of 1920, while at Saranac, the first attack of severe epigastric pain set in. It penetrated to the back, was taken for an acute indigestion, although the possibility of gall stones was also considered. The second attack came on June 5, 1921. Severe pain on right side, the entire right side was rigid and very tender, so that it was difficult to differentiate between gall-bladder and appendix. Temperature up to 103°; while white cell blood count was 12,000, 84 per cent polynuclears, 16 per cent lymphocytes. Light jaundice. Fever and tenderness gradually disappearing. While in bed for about three weeks undergoing a modified "Carlsbad cure" with application of heat to the right upper side, a sudden attack of very severe pain on the left side set in, radiating into the scrotum and left thigh, bearing all the earmarks of a renal colic. No red blood cells or concretions were found in the urine. He was greatly benefited by the Carlsbad treatment, and went to the mountains for the whole summer and remained free of pain until September, 1921, when renewed attacks of very severe pain in the upper abdomen set in, radiating to the middle of the back and to the right shoulder. They became more frequent, finally occurring every day. The pain was usually of such a severe character that no medication except morphin hypodermically would give relief. At no time were fever or jaundice present. The roentgen-ray showed stones in the gall-bladder.

October 5, 1921, Dr. John Erdman removed the gall-bladder with 77 stones and 5 stones from the common duct. The gall-bladder was thickened, firmly adherent to the liver and to the surrounding tissues and was separated with great difficulty. No signs of acute inflammation were found. Cultures from the gall-

bladder were sterile. Free flow of bile was secured by drainage. Uneventful recovery until the twelfth day after the operation (one day after removal of the drainage tube from the bile duct) when the patient suffered again an attack of very severe abdominal pain of the same character as before. A week later he had a similar attack. From then on the attacks occurred more frequently, finally every day and even two or three times within twenty-four hours. The pain, excruciatingly severe, varied in its location. At times it was felt in the middle of the abdomen, radiating toward the back or the chest and in the latter event causing severe dyspnea; at other times it would start in the right upper side radiating toward the groin. Not infrequently the paroxysm was preceded by painful peristalsis and gaseous borborygmi. On several occasions, particularly with the onset of phosphaturia (see further below) very severe pain occurred on the left side, shooting into the bladder. It was associated either with great difficulty to pass urine, or with very frequent voiding of small quantities of urine. This dysuria was observed at other times with clear urine.

The paroxysms came on at irregular intervals, at any time during the day or the night. They were not in any way related to meals, were occasionally alleviated by an enema and alvine evacuation, and were, as a rule of such a severity, that none of the many drugs tried would give relief except morphin hypodermically administered.

With numerous attacks occurring over a period of about four months no fever or any other signs of inflammation were ever observed.

The blood picture was that of secondary anemia. On January 12, 1922, the hemoglobin was 75 per cent, red blood cells 4,368,000; leukocytes 7200; polymorphonuclears 73 per cent; lymphocytes 27 per cent. Wassermann negative.

The blood pressure was low, systolic 90 to 100, diastolic 40. No disorders of the heart.

Fluoroscopic combined with serial roentgenographic examination of the gall-bladder region, stomach and duodenum done on November 21, 1921, did not reveal any evidence of stones in the biliary ducts. The report of the roentgenologist continues as follows:

"We gave the patient the usual barium meal, and examined him in all different positions, both erect and prone. We were at once struck by the very vigorous hyperperistalsis, marked writhing contractions were seen almost immediately and continued through the entire observation. On manipulation under the screen, we found evidence of adhesions binding down the prepyloric region of the stomach and the first portion of the duodenum. On the upper border of the bulbous there is a persistent defect.



"In postoperative cases, one has great difficulty in deciding what is producing such a deformity to the outline of the first portion of the duodenum. It must be either one of two things, adhesions or true ulceration. Considering the character of the shadows, the persistency of the deformity, and the fact that we had such very marked hyperperistalsis, it would seem to be some ulceration."

After an examination of the entire urinary tract on December 13 the report reads:

"I fail to find any evidence of nephrolithiasis, nor do we find any shadows that are even suspicious of a stone in either ureter. In the bladder, well down toward the symphysis, we see some irregular shadows which suggest calcareous deposits in close relation to the prostate.

"The left kidney seems somewhat enlarged but is normal in size and position. The right kidney is not clearly outlined owing to the presence of gas and fecal matter in the proximal colon.

"If you will refer to my report of Mr. M's examination of November 21, you will note that I referred especially to the presence of a very vigorous hyperperistalsis. I also reported a distinct deformity to the first portion of the duodenum and in my conclusion stated that I believed the man had a duodenal ulcer."

Gastric analysis after test-breakfast showed nothing abnormal: free acid, 36; total acidity, 58.

Stool as a rule very scanty, dry hard scybala, often passed only with great difficulty, denoting spastic constipation. At other times the stool was copious, mushy, acid, reminding one of a pancreatic stool, without, however, showing impaired digestion of fat, starches or meat. No occult blood in feces.

Duodenal drainage on January 27, 1922; tube inserted at night; next morning with fasting stomach after application of 50 cc of 20 per cent magnesium sulphate solution, immediate free flow of bile. First portion dark and thick (absence of gall-bladder); during the following six hours about 500 cc of bile were gained, light yellow, viscid, without sediment, showing on microscopical examination neither leukocytes or epithelial cells, nor crystals. Culture sterile.

Whenever I had occasion to see the patient, I was impressed by a marked tendency to spastic conditions. At various examinations abdominal muscles between the attacks were found contracted and rigid; during attacks the whole abdominal wall appeared board-like in tetanic contraction. Having his attention aroused, patient reported, that at this period during meals, he frequently had to drop fork or knife on account of cramps in his hands. When walking he often had to stop for a while to let pass severe cramps in calves or feet. Even when in bed the abdominal paroxysm was frequently preceded or followed by cramps in calves or feet, often of very great severity. At one time (middle of January, 1922), he felt severe pains in the little fingers and in the big toes. I have already mentioned the spastic bladder condition.

This impression of spasmophilia was strengthened by findings of disordered calcium metabolism. While the urine as a rule showed nothing abnormal, during the month of December, 1921, for several weeks regularly, and in January, 1922, for a while intermittently, the urine was of peculiar and unusual character; freshly passed, the urine was turbid, strongly alkaline, had a very pungent odor of ammonia and a very heavy whitish powdery sediment, which the microscope revealed as consisting partly of amorphous material, to a greater extent, however, of triple phosphate crystals, while there were no cellular elements pointing to an inflammation of the urinary tract, and no indication of bacterial fermentation.<sup>10</sup>

At a time when the urine had been clear for a while, a study of the calcium metabolism by Dr. A. Bernhard, pathological chemist to the Lenox Hill Hospital, showed the following:

TABLE I.—METABOLIC STUDY OF CALCIUM.

	Total quantity.	Calcium as CaO.
January 20 to January 21, 1922:		
Excretion:		
Urine . . . . .	1000 cc.	0.335 gm.
Stool . . . . .	256 gm.	3.910 "
Total . . . . .		4.245 gm.
Intake (milk diet) . . . . .		3.900 gm.
Loss of calcium during first day . . . . .		0.345 gm.
January 21 to January 22, 1922:		
Excretion:		
Urine . . . . .	1450 cc	0.529 gm.
Stool . . . . .	249 gm.	8.510 "
Total . . . . .		9.039 gm.
Intake (milk diet) . . . . .		2.500 "
Loss of calcium during second day . . . . .		6.539 gm.
Average daily calcium excretion in urine <sup>11</sup> for two days . . .		0.432 gm.
Average daily calcium excretion in feces <sup>12</sup> for two days . . .		6.210 "

*Chemical Examination of Blood.* Urea nitrogen, 22 per cent; creatine, 1 per cent; uric acid, 5 per cent; sugar 0.08 per cent; calcium, 6.2 per cent; (normal calcium, 5.3 to 6.8 per cent.)

From a report of the status of the nervous system taken on January 21, 1922, I quote the following:

Pupils equal, both react to light, accommodation and consensually. There is no disorder in the territory of the facial nerve. The tongue is coated, but protrudes in the median line, and shows

<sup>10</sup> Regarding the relation of phosphaturia to disordered calcium metabolism, I refer to F. Ueber (Ernährungs- und Stoffwechselkrankheiten, Ed. 2, 1914; chapter on Phosphaturia, p. 469).

<sup>11</sup> Normal excretion of Ca in urine 0.1 to 0.4 gm.

<sup>12</sup> Calcium elimination by feces normally between 60 to 90 per cent of the amount ingested, while in this case, with only 6.4 gm. intake, there was an excretion of 12.42 gm. instead of 5.7 gm. at the utmost.

no atrophy or fibrillation. No motor disorder manifest in the entire body; no sensory disturbance except as indicated below. Deep reflexes markedly increased; superficial reflexes are normal except for an absence of the upper and lower abdominal reflex on both sides. Some hypalgesia over the left lower abdominal region. Mechanical excitability of the muscles of both forearms, markedly increased with a pronounced idiomuscular ridge easily produced. Mechanical excitability of right lower abdominal muscles markedly increased. Electrical reactions normal except in the muscles of the right lower abdominal region (scar territory) in which there is a reduced faradic excitability and anodal closure contractions greater than cathodal closure contractions, in the abdominal muscles due to the incision made in the right lower abdominal region.

Although this examination showed no electrical hyperexcitability of the peripheral nerves at the time of the examination, the various manifestations of tetanoid contractions of peripheral muscles before and after this examination suggested the probability that we were dealing here with a similar hyperexcitability of the abdominal vegetative nerves with consequent spasm and pain, as were indicated by the finding of intense gastric hyperperistalsis during the roentgenological examinations. Attempts to correct this condition by dietetic and various medical treatments, including the administration of parathyroid and calcium chloride by mouth, proved futile, so that, when at the end of January the paroxysms of pain became more frequent and for several days required two, to three morphin injections within twenty-four hours, we decided to open the abdominal cavity once more, considering the possibility that a remaining gall stone, cancer, or another undiagnosed local lesion might be the provocative agent. At the wish of the patient the operation was set for a certain date, when a complete change of the picture necessitated an earlier operative interference. On February 2, with an atrocious attack of pain particularly severe in the back, fever up to  $102^{\circ}$  and pronounced jaundice were observed; the urine was full of bile, the stool clay-colored (careful searching of the stool for a number of days failing to find stones).

**OPERATION.** February 3, 1922. Dr. John Erdman found dense adhesions at the site of the removed gall-bladder impinging upon the common duct. The common duct was readily exposed and found fairly dilated. Upon opening the common duct, a considerable amount of purulent material was extruded, a scoop and catheter, the latter the size of number sixteen French readily passed through into the duodenum. No stones in common or hepatic ducts; no signs of peptic ulcer. Head of pancreas considerably swollen and indurated; choledochostomy was completed by sewing the catheter into the duct and drainage established. Culture of common duct content showed pure cultures of *B. coli communis*.

For two days an uneventful course, except for frequent vomiting. From the third day on the spastic tendencies returned once more. For a number of days very frequent painful urination of clear urine was present and a much more annoying symptom, that is singultus, which, with short intervals, continued during eleven days, greatly sapping the patients strength and unrelieved by any sedative, atropin, alkalies, acids and other drugs. Morphin injection gave relief for a few hours, likewise gastric lavage, this was for several days performed two and three times a day, always removing large quantities of fluid with turbid masses. An attempt to employ duodenal tubing miscarried, the tip remaining in the stomach.

Considering the evidence of disordered calcium metabolism I advised intravenous injections of calcium chloride, 5 cc of a 10 per cent solution, for three days given twice a day, then once a day, then every other day and finally twice a week. Altogether 20 injections were given. After the first injection of calcium chloride the singultus stopped, appetite returned and food intake was tolerated. From now on rapid recovery followed, patient regaining strength, remaining free from all discomfort and adding up to the middle of April, 20 pounds in weight. It is worthy of note that with all the very severe disturbances the lung condition remained stationary and inactive.

**Comment.** The inflammation of the dilated common duct found at operation was of recent date, with fever and jaundice of about thirty hours' duration, while only a week before duodenal drainage had produced a free flow of bile carrying no signs of inflammation. Since no stones were discovered and Vater's papilla proved wide open, it is not stretching imagination too far, to consider the acute cholangitis a result of severe spasm involving the sphincter of the common duct, which also caused acute pancreatitis by a flow of infected bile into the pancreas.

Spasticity is a predominant feature in the history of this patient. From childhood on pronounced tendency to hiccoughs existed and during the period of observation frequent cramps were observed in various parts of the voluntary neuro-muscular apparatus.

Combined with spasmophilia we found evidence of disordered lime metabolism. At one time there was an unusual type of phosphaturia and at another period an increased discharge of lime from the intestines.

*Disordered Calcium Metabolism and Visceral Tetany.* The association of disturbed calcium metabolism and tetany after experimental and operative removal of the parathyroids led to the conception that a change in calcium content causes the increased irritability of the neuromuscular apparatus. There is still a great divergence of opinion regarding the actual relation of parathyroid deficiency and of disordered calcium metabolism, also

regarding the character of the calcium disorder. Some authors assert that in this deficiency the calcium content of the blood is low, while others maintain that the total amount of calcium present in the blood is not as important, as is the quantity of calcium present as free calcium.<sup>13</sup> However that may be, when the parathyroids are involved, we can well imagine, that functional parathyroid insufficiency (of whatever origin) may account for temporary states, both of disordered calcium metabolism and of tetany (analogous to paroxysmal tachycardia). Barker and Sprunt<sup>14</sup> claim that temporary tetany may occur without defective functioning of the parathyroid glands. But let chemical changes making for spasticity once develop in the system, be this an effect or not of parathyroid malfunction, these changes may not only increase the irritability of the voluntary neuromuscular apparatus, but may in a similar way affect the vegetative nerves, a condition for which the term "visceral tetany" has been suggested. In a very interesting study Melchior<sup>15</sup> discusses the very great variability of the picture, which visceral tetany may present according to which part of the vegetative nervous system is particularly involved at a given time.

In our case the spasm occurring shortly before the onset of the acute cholangitis and pancreatitis must have involved Oddi's muscle. Whether during the preceding months the severe abdominal paroxysms were confined to the same locality is very difficult to determine. The varying location and irradiation of the pain point to a changing location of the spasm, for which the picture of renal colic with the onset of phosphaturia gives an illustration. It is possible that the roentgen-ray examination during attacks might have visualized the seat of spasm at a given time. Where this was done it yielded interesting results. Melchior in the paper just quoted reproduces the roentgenogram of a patient suffering from gall stones (later removed by operation), which taken during an attack of pain shows a true gastrospasm, the middle portion of the stomach being tightly contracted into a sausage-shaped form. Three quarters of an hour later the same picture was seen. A roentgenogram taken two days later during a pain-free period revealed a normal non-ptotic hook-formed stomach with good tone and with a completely filled out middle portion and antrum. This and similar experiences by Melchior and others should guard us against drawing from roentgenograms taken between attacks, too close conclusions regarding the seat of pain and spasm.

*Visceral Tetany and Pulmonary Tuberculosis.* There is one more interesting feature in the history of this case, the combination

<sup>13</sup> Van Paassen: Nedrl. Tijdschr. v. Geneesk. (Haarlem), 1921, 65, 1162; Abstract, *Endocrinology*, 1922, 6, 132.

<sup>14</sup> *Endocrinology*, 1922, 6, 1.

<sup>15</sup> Mitt. a. d. Grenzgeb. d. Med. u. Chir., 1921, 34, 400,

of visceral tetany with pulmonary tuberculosis. It is a well known fact, that pulmonary tuberculosis is frequently associated with states of gastric irritation and with peptic ulcer. Singer<sup>16</sup> recently reported postmortem findings of peptic ulcer with pulmonary tuberculosis. They showed degeneration and neurotic atrophy of the vagus. Singer considers the anatomical changes of the vagus a product of the tuberculous process. In cases still devoid of manifestations of a lung involvement, he attributes the earlier state of functional vagus derangement to a tuberculous disposition. These cases present only symptoms of gastric irritation and Singer designates the gastric syndrome the sign of latent tuberculosis. One may gain a different aspect of the combination, by considering the possibility, that both, the lung and the gastric disease, are the result of the same underlying general disturbance. The same constitutional makeup, the so-called asthenic habitus, predisposes equally to pulmonary tuberculosis and to derangements of the vegetative nerves. It is possible, that here also disordered calcium metabolism plays a part. We have just discussed its relation to visceral tetany and it may be added that French clinicians lay great stress on demineralization, especially upon the increased discharge of calcium and magnesia as one of the basal factors in the development of pulmonary tuberculosis. One may perhaps find some support for this conception in the favorable reports of the treatment of tuberculous conditions by the systematic intravenous injection of calcium chloride solutions,<sup>17</sup> the same as those which were employed in our case.

*Calcium Therapy.* Finally a few remarks about calcium therapy. I frequently use calcium in the treatment of irritative disorders of the digestive organs, employing large doses of lime water, calcium lactate, the various calcium phosphate preparations, from among which, for a while I used to favor the tribasic calcium phosphate, specially prepared, for it is difficult to procure. During the last few years I have been giving, with preference calcium chloride, a teaspoonful of a 20 per cent solution of crystallized calcium chloride in distilled water, to be taken in half a tumbler of water in the course of the principal meals. I have seen some favorable results, for example in periodical painful gastric hyperacidity, which in certain cases was promptly relieved by the calcium solution. I advise patients subject to periodic hyperacidity and to periods of active ulceration to continue the calcium medication over a course of months, anticipating its prophylactic effect in the same way as it is supposed to act as a preventive of hay-fever.<sup>18</sup> The beneficial effect of a long continued milk diet

<sup>16</sup> Arch. f. Verdauungskr., 1921, 28, 131.

<sup>17</sup> Maendl: Ztschr. f. Tuberc., Leipzig, 1921, 35; Abstract, Jour. Am. Med. Assn., 1922, 78, 137, giving instructions as to technic. See further: Ringer, P. H., and C. L. Minor (Am. Rev. Tuberc., 1922, 5).

<sup>18</sup> Emmerich, R., and Loew, O.: München. med. Wchnschr., 1915, 62, 41.

in peptic ulcer and other irritative disorders of the digestive tract is probably in part due to the high calcium content of the milk.

In our case we employed before the second operation both milk diet and the calcium chloride solution, although only for a short period. They failed to make any impression upon the tendency to these severe paroxysms. After the second operation, however, the intravenous calcium administration seemed to stop the very annoying hiccough and the associated retroperistalsis of the upper digestive tract. I have no intention of overstating the importance of a single observation, but this experience should certainly encourage further trials of intravenous calcium therapy in cases of visceral tetany.

Lime therapy is empirical and will remain so until we know more about calcium metabolism and its disturbances. So far our knowledge is scanty. Here is a large field for investigation with the vista, that modern chemistry will establish a solid foundation for the study of calcium metabolism, disorders of which may prove to be the underlying constitutional derangement in the development of local diseases of the digestive tract, as gout is in acute inflammations of joints and diabetes in a number of cases.

In our case the spasm occurring in the  
 Muto. cholangitis.

## THE CHEMISTRY OF PSEUDOCHYLOUS ASCITES AND OTHER TYPES OF EXUDATES.\*

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AND

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MILKY effusions into the serous cavities are classified into three types: as presented by Rolleston<sup>1</sup> and more recently by Huber<sup>2</sup> and Bradbury.<sup>3</sup> These comprise: (1) *The true chylous*, due to the presence of chyle; (2) *the chyliform or fatty*, containing emulsified fat as the result of a fatty degeneration of cellular elements, and (3) *the pseudochylous*, in which the opacity of the fluid is not attributable to a fatty emulsion. Wallis and Schölberg<sup>4</sup> do not consider that groups two and three are distinguishable and preferred to consider them both under the term "pseudochylous."

However, even this differentiation is not accepted by Gandin,<sup>5</sup> who does not believe that the negative chemical tests for fat in the pseudochylous fluids disprove the assumption of the fatty

\* Read at the meeting of the American Association for Clinical Investigation, May, 1922.

nature of suspended molecular granules; he considers therefore the terms chyliform and pseudochylous as superfluous.

According to Lee<sup>6</sup> experimental ligation of the thoracic duct in cats leads to the development of collateral lymph paths or new venous anastomoses; accumulation of free fluid in the peritoneal cavity and thorax did not occur. It has for years been assumed that complete or partial obstruction of the duct may induce a true chylous ascites. This experimental work of Lee still further shows our ignorance as to the origin and pathogenesis of even true chylous ascites, though the author admits that "one cannot claim with absolute surety that ligation of the thoracic duct in the human subject would prove equally innocuous."

The opacity of the pseudochylous type of effusion is due to the presence of lecithoprotein, according to Wallis and Schölberg;<sup>4</sup> the lecithin is associated with the globulin fraction. These writers have reviewed 173 cases of milky effusion in the literature, of which 71 were "probably of pseudochylous type." As causes, in order of frequency for this group, they found (1) malignancy, (2) nephritis, (3) cirrhosis of the liver, and (4) tuberculosis.

In reviewing the literature, one is struck by the paucity and insufficiency of the chemical data in even the more recent case reports of milky effusions. Again, emphasis is placed particularly on the differentiation of the types of milky effusions, and little or no attention is given to a comparison of these from a chemical standpoint with the ordinarily encountered transudates or exudates. Bradbury<sup>3</sup> has tabulated from the modern literature up to 1918, the chemical, gross and microscopical characteristics of chyle (9 cases), chylous fluids (10 cases), and pseudochylous fluids (13 cases); the fluids were typed according to the criteria of Wallis and Schölberg with consideration of the clinical descriptions. Recent case reports of milky effusions include contributions by Udaonda and Castex,<sup>7</sup> Udaonda and Carulla,<sup>8</sup> Hendricks,<sup>9</sup> Casaubon,<sup>10</sup> Traub,<sup>11</sup> and Tuohy.<sup>12</sup>

The clinical features and the pathological findings in the case of malignancy with milky ascites, which came under our observation, are quite typical. For comparison, data on 3 cases with ascites where paracentesis was done about the same time are included (Table I). The analysis of the fluid aspirated from the brain tumor case will be discussed later in the paper; these figures are given in the last column of the table. The case histories follow:

CASE I.—Watson; aged seventy-six years; widow; clinic No. 9671; admitted December 14, 1921; for five years sudden attacks of nausea and vomiting followed by slight icterus; no colic; radical operation for carcinoma of mamma, August, 1920. Present illness began in November, 1921, with sense of distress and occasional



sharp pain in right upper quadrant; gaseous eructations and constipation; anorexia, loss of weight and strength. On examination some cachexia but no jaundice. Abdomen tense and resistant; free fluid present. No anemia. Gastric subacidity. No occult blood in stools. Gastric series after barium meal negative. Paracentesis, December 17, yielded 3400 cc of milky yellow fluid (Watson I); roentgen-ray therapy. Death January 6, 1922, from progressive cachexia and anuria. Second aspiration one hour post mortem, revealed about 1000 cc reddish-brown fluid (Watson II). Postmortem examination revealed primary carcinoma of gall-bladder with metastases to liver, ovary, pleura, lung and peritoneum with hydroperitoneum.

CASE II.—Shoemaker; aged twenty-five years, male; clinic No. 9447; admitted October 8, 1921; rheumatic fever in 1914 with endocarditis followed by gradual onset of cardiac decompensation, until by July, 1921, he was bedridden and remained so until death. Examination revealed an old mitral and aortic insufficiency with general anasarca. On December 2, 1921, paracentesis of 850 cc of cloudy straw-colored fluid and again on December 6, 1921, 3230 cc of similar gross appearance (See Shoemaker). Third paracentesis January 9, 1922, of 330 cc. Death January 10, 1922. Autopsy revealed a healed mitral and aortic endocarditis, an obliterative pericarditis and marked hypertrophy and dilatation of heart.

CASE III.—Ball; aged fourteen years, female; clinic No. 9710; admitted December 28, 1921. Scarlet fever in 1915, and chorea in 1917. Tonsillitis in November, 1921; liability to winter bronchitis since pneumonia in infancy. No arthritis. Present illness began November 27, 1921, with edema of legs; on December 11, pain in right upper quadrant where a hard mass could be felt, called a tumor of the liver by the home physician. Examination revealed general anasarca, an enlarged heart, embryocardia and a short systolic bruit at apex; pulmonary edema; an enlarged liver and marked ascites; no jaundice; no anemia; normal urine. Paracentesis on December 30, of 1325 cc of light straw-colored fluid (See Ball). Patient removed December 28, 1921, against advice, with a tentative diagnosis of chronic adhesive pericarditis and cardiac decompensation (Pick's disease).

CASE IV.—Mohs; aged twenty-six years, painter; clinic No. 8907. Admitted April 29, 1921. Scarlet fever at sixteen, followed by arthritis of ankles; second attack of rheumatic fever at nineteen. Since then dyspnea, palpitation and edema upon exertion. All symptoms greatly increased since the spring of 1920 and have rendered him a chronic invalid. Examination revealed marked

cyanosis, general anasarca, auricular fibrillation, a much dilated heart without murmurs, an enlarged liver, ascites, albuminuria, etc. On August 18, he developed signs of a mediastinitis, which gradually subsided; for mechanical relief an abdominal paracentesis was done January 9, 1922, and 3000 cc of dark turbid fluid obtained, (see Mohs). Death January 17. Autopsy revealed an enormously dilated heart with an obliterative pericarditis, and a very extensive myocarditis.

**DESCRIPTION OF THE ASCITIC FLUIDS.** *Watson I.* The fluid was milky with a very slight yellow tinge. It had no odor. On standing, a slight separation of fibrin occurred; this enmeshed the formed elements—a few fresh red cells, lymphocytes and epithelial cells. On standing at room temperature without aseptic precautions, the fluid was somewhat resistant to putrefaction for several days; with increasing bacterial growth, part of the protein separated as a white flocculent layer on the surface, a phenomenon which might be mistaken for a cream layer.

*Watson II.* The fluid was removed at autopsy one hour after death. It was somewhat less opaque than the previous specimen, but otherwise was not different.

*Shoemaker.* This fluid had the appearance of that of an ordinary ascites; it was somewhat greenish and turbid. A slight separation of fibrin occurred.

*Ball.* When received for analysis, the specimen was three days' old, and considerable bacterial growth was evidenced on microscopical examination of the slightly flocculent sediment. It was of a yellow-green color and without odor. As the fluid was not fresh, sugar and non-protein nitrogenous constituents were not estimated.

*Mohs.* The fluid was of the ordinary character and sediment. A slight formation of fibrin obtained.

*Analytical Methods.* *Proteins:* By heat coagulation and weighing the water, alcohol, and ether washed precipitates; or by Kjeldahl nitrogen determinations on the tungstic acid (Folin) precipitates; globulin figures are by difference.

*Fatty Acids.* Bloor's method.

*Lecithin Phosphate Acids.* Bloor's method.

*Cholesterol.* Autenrieth and Funk.

*Glucose.* Folin and Wu.

*Non-protein Nitrogen.* Micro-Kjeldahl according to Folin and Wu, but titration of the distillate with N/100 alkali.

*Urea Nitrogen.* Urease treatment and aeration with N/100 sulphuric acid, and titration with N/100 sodium hydroxide.

*Creatinine and Creatine.* Folin and Wu.

*Chlorides.* Rappley's method.

*Calcium.* Halverson and Bergheim, Tisdall and Kramer.

Determinations of the lipins, sugar, and urea were immediately started on receipt of the specimens in the laboratory. Samples of the fluids with chloroform added as a preservative were kept in the refrigerator to be used for the other determinations, which were promptly undertaken.

TABLE I.—CHEMICAL COMPOSITION OF THE ASPIRATED FLUIDS.

(The analytical figures are gm. per hundred cc or mgm. per hundred cc.)

	Watson I.	Watson II.	Shoemaker,	Ball.	Mohs.	Kinsolver.
Specific gravity, 20°	1.020	1.025	1.014	1.018	1.018	1.037 (H <sub>2</sub> O = 1)
Total solids	5.340	6.362	2.950	5.000	4.683	8.502
Ash	0.595	0.683	0.625	0.641	0.641	0.760
Total protein	3.931	3.813	1.922	3.806	3.376	6.758
Albumin	2.150	2.575	0.790	2.217	1.640	4.006
Total "globulins"	1.781	1.238	1.132	1.589	1.736	2.750
Total fatty acids	0.660	0.480	0.310	0.300	0.300	0.320
Lecithin, H <sub>3</sub> PO <sub>4</sub> *	82.500	53.300	16.700	22.200	23.000	50.800
Net fatty acids†	0.190	0.170	0.210	0.170	0.170	0.030
Cholesterol	0.088	0.080	0.048	0.048	0.032	0.144
Glucose	0.100	0.105	0.100	...	0.148	0.060
Non-protein nitrogen	36.500	350.000	42.000	...	98.000	40.000
Urea nitrogen	10.000	180.000	14.000	...	33.600	15.000
Uric acid	3.700	14.000	3.900	...	8.000	4.350
Creatinine	1.200	3.800	0.830	...	1.080	0.830
Creatine‡	2.000	9.500	1.670	...	2.100	1.500
Chlorides as NaCl	0.600	0.630	0.685	0.670	0.620	0.630
Calcium	7.300	7.600	7.000	7.500	7.000	9.000

\* These figures multiplied by 8 gives approximate lecithin contents.

† After subtracting lecithin fatty acid.

‡ As creatinine.

The data on the Watson fluids (Table I, columns 1 and 2) when judged by the "determining points" of Wallis and Schölberg, are consistent with the criteria for the pseudochylous type except for the high specific gravity and protein content (Table II). However, the source of the effusion must be considered; pleural, peritoneal, cutaneous and cerebrospinal fluids show relative differences in the protein concentration. Again, differentiation by the protein content or the specific gravity of pseudochylous and chylous fluids should be very questionable. Lymph concentration in protein would depend on the permeability of the endothelial walls of the vessels and would be influenced by toxic injury to these.

The proportion of serum albumin to serum globulin might vary according to quantitative differences in the blood proteins (Umber<sup>13</sup>) though influenced by the relative viscosity which determines the ability of these proteins to pass through the capillary walls (Oswald<sup>14</sup>). Accordingly, it would be expected that effusions in cases where the blood plasma contained little serum albumin (amounts only slightly over 0.1 per cent have been noted) would

have a low total protein content with a very high ratio of the globulin to the albumin. Such fluids are found in the literature. Epstein<sup>15</sup> even reports one peritoneal fluid (nephritic) of very low total protein content (0.285 per cent) in which serum albumin was not present. It may be said that attempts have been made to correlate the proportion of globulin to albumin in ascitic fluids with the clinical conditions which invoked these (Joachim<sup>16</sup>).

TABLE II.—CRITERIA OF WALLIS AND SCHÖLBERG APPLIED TO OUR CASE (WATSON).

(The *plus* signs mark the characters that obtain for our milky ascitic fluids Watson I and II.)

	Chyle.*	Chylous fluids.	Pseudochylous fluids.
Specific gravity . . .	1.022	+ Over 1.012	Under 1.012.
Total solids . . .	6.785	+ 4 per cent or more	2 per cent or less.
Total protein . . .	3.640	+ 3 per cent or more	1 to 3 per cent.
Serum albumin . . .	...	+ Mostly.	
Serum globulin . . .	...	Traces only	+ Appreciable amounts
Fats . . . . .	2.990	0.4 to 4 per cent	+ Low.
Lecithin . . . . .	0.310	Traces only	+ Characteristic.
Cholesterol . . . .	0.490	Always present	+ Occasional.
Sugar . . . . .	...	0.36 to 0.00*	0.196 to 0.00.*
Salts . . . . .	0.740	As in chyle	As in lymph.
Color . . . . .	...	Yellowish	+ White.
Opacity . . . . .	...	Same each tap	+ Varies each tap.
Odor . . . . .	...	Slight, like food	+ None.
Microscopic cells . .	...	Very few	+ Vary, may contain fat.
Microscopic fat . . .	...	Fine fat globules	+ Granules, not fat.
Cream layer . . . .	...	Usual	+ Not usual.
Freezing point . . .	...	About -0.51	-0.56 to -0.61.
Sediment . . . . .	...	None	+ Usual.

\* Bradbury's compilation.

The most striking of the chemical "determining points" seem to be (1) the high content in lecithin, which is associated with the so-called globulin fraction,\* (2) the low fatty acid figure and the uniformity of the fatty acid content after allowing for the lecithin fatty acid, and (3) the low cholesterol figures. True chylous fluids would seem to contain cholesterol in quite appreciable amounts, probably because of absorption of food and bile cholesterol from the intestine into the lacteals. Mueller<sup>17</sup> found that there resulted an increase in both cholesterol and cholesterol esters in the chyle of dogs when either one was added to the diet.

It may be noted that the milky ascites differs from our other peritoneal fluids particularly in the higher content of lecithin-phosphoric acid and of cholesterol; however, the cholesterol con-

\* The filtrates containing the serum albumin after precipitation of the fluid (five-fold diluted) with an equal volume of saturated ammonium sulphate solution were water clear.

tent of the Watson fluids is lower than that of blood plasma or even than that in the acute exacerbation of pernicious anemia. Inasmuch as Horiuchi<sup>18</sup> has shown that experimentally induced lipemia in rabbits may increase the plasma lecithin up to seven and the cholesterol up to eight times the normal values, an explanation for the formation of transudates that are pseudochylous is suggested when such conditions obtain.

Calcium in excess in protein combination is apparently not responsible for any of the opacity of the pseudochylous fluid, being present in all of the specimens in but little less concentration than in normal blood plasma. Wallis and Schölberg's figures (recalculated as calcium) are 18 and 12 mgm. per cent respectively for their white fluids in order of opacity, and but 2 and 3 mgm. per cent for the less milky specimens; they do not discuss their calcium results in this connection.

Of particular interest are the very high non-protein nitrogenous constituents in the second Watson fluid, due to anuria; a moderate degree of non-protein nitrogen retention obtains for Mohs also.

Kast and Killian<sup>19</sup> found that many advanced cases of malignancy, possibly as the result of the toxemia, give the chemical blood picture of moderately severe nephritis with a hyperglycemia and lowered carbohydrate tolerance; the termination of some of their cases was typically uremic.

Denis and Minot<sup>20</sup> have shown that the non-protein nitrogenous substances in transudates and exudates vary with the concentrations in the blood; they did not work with nitrogen retention cases. Recently Weiss and Garner<sup>21</sup> reported a case of nephritis with unusually high progressive nitrogen retention; their data include urea nitrogen determinations, which approximate the blood findings,\* on the cerebrospinal and pericardial fluids. Our total non-protein nitrogen estimation on the Watson II, specimen and on Mohs also is relatively very high as compared with the urea nitrogen figure; the residual nitrogen probably represents amino-acids, and a separation of characteristic crystals of leucin and tyrosin actually occurred in the second pseudochylous fluid.

A specimen of a fluid aspirated from the brain was subjected to the same analytical procedures as were the ascitic fluids. A brief summary of the clinical findings for the case (Kinsolver) follows:

CASE V.—Kinsolver; aged twenty-five years, farmer; clinic No. 9730; admitted January 4, 1922; first noted headache, nausea and vomiting November 1, 1921, which gradually recurred at more frequent intervals. In February, 1921, syncopal attack without convulsion. Subsequently three or four attacks of loss of consciousness and generalized convulsions beginning in the legs;

\* The total non-protein nitrogen twelve hours before death was 401 mgm., of which urea nitrogen represented 75.8 per cent.

some failure of vision and mental irritability. Examination by Dr. van Epps revealed a marked Romberg sign and reeling gait; coarse tremor of hands. Marked bilateral choked disk, more advanced in right. Blood and spinal fluid negative in all respects. On January 13, 1922, under local anesthesia a small trephine opening near midline in frontal region was made. A needle was passed through the intact dura for one and one-eighth inches and entered an area containing fluid under pressure. This was removed by the two-way syringe and equal amounts of air were introduced without discomfort. The stereoscopic plates revealed a large cyst in the frontal region taking origin at the base of the brain in the region of the pituitary. This had been tapped instead of the ventricles. As the site of the cyst rendered the removal extremely hazardous, the patient was discharged temporarily relieved of his pressure symptoms.

The specimen was received in the laboratory promptly after aspiration and was in volume 45 cc. It was a slightly orange-yellow fluid, very clear, and without sediment except for glistening suspended cholesterol crystals. It did not clot, even on standing for the period of the analytical examination. An occult blood test (Meyer's) was negative.

The analytical data (Table I, the last column) show a fluid similar to blood serum of rather high specific gravity and total solid content, of which the protein approximates 80 per cent. In spite of the cholesterol crystals in suspension, the cholesterol content is not above that of blood plasma. Allowing for the fatty acid combined as lecithin (as dioleal lecithin), the neutral fat content must be practically *nil*. The amount of sugar present is about that of normal cerebrospinal fluid. The uric acid is a little high as compared with normal blood. The presence of cerebrins could not be demonstrated.

The xanthochromia and the high protein content of the specimen recall the fluid compression of the types described for the spinal cord as the syndromes of Froin and of Nonne (Sprunt and Walker<sup>22</sup>). The fact that the cerebrospinal fluid was essentially normal indicates an intraventricular cul-de-sac or a cyst. Wells<sup>23</sup> states that the presence of cholesterol crystals in aspirated fluids may be attributed either to relatively old processes involving cellular degeneration, or to the resolution of a large blood extravasation. It is probable that we are dealing with a degenerating brain tumor replaced by a gradually concentrating transudate. The fibrinogen has either not passed into the fluid or has been deposited as fibrin on the wall of the cavity. The xanthochromia should be due to the ordinary plasma pigments. However, the similarity of the glucose content to that of cerebrospinal fluid is perhaps not without significance.

Finally, we would recommend the more frequent complete chemical investigation of all transudates or exudates because of the valuable diagnostic and indeed prognostic assistance sometimes obtained.

**Summary and Conclusions.** The chemical composition of a milky peritoneal fluid from a case of malignancy, and the comparative data of three cases with serous ascites are presented.

The milky effusion is characterized by its high content of lecithinphosphoric acid and to a lesser degree of cholesterol. Net fatty acid figures are low for all the fluids.

Calcium in protein combination is not responsible for the opacity of the fluid.

Milky fluid obtained at necropsy one hour after death following three days of anuria has a non-protein nitrogen partition such as is found for the blood in severe retention cases.

It is concluded that the milky fluid obtained in our case is a true pseudochylous ascites.

A specimen of a yellow fluid aspirated from an intra-ventricular cyst or ventricular cul-de-sac of the brain was subjected to the same analytical procedures as were the ascitic fluids. The figures are included in this report.

*Addendum.* Since the report was sent to this journal, we have studied the aspirated contents of a cyst of two months standing in the groin of a man, aged twenty-five years, (Case F. A., No. 51486). About 150 cc of a viscous, slightly turbid, light straw-colored fluid were obtained. Smears, cultures and guinea-pig inoculation were negative. The fluid is of particular interest because of its content in mucin, when an epithelial origin can hardly be presumed in this instance. The mucin was identified by precipitation with acetic acid and yielding on acid hydrolysis abundant reducing substances without sulphate formation. The glucose content of the fluid was notably low. Analytical figures follow:

#### COMPOSITION OF MUCIN-CONTAINING FLUID ASPIRATED FROM THE GROIN.

Specific gravity . . . . .	1.030	Cholesterol . . . . .	0.22
Total solids . . . . .	7.890	Glucose . . . . .	0.02
Ash . . . . .	0.570	Non-protein nitrogen . . .	30.80
Total protein . . . . .	5.890	Urea nitrogen . . . . .	14.70
Albumin . . . . .	3.250	Uric acid . . . . .	5.40
Globulins . . . . .	1.080	Creatinine . . . . .	1.50
Mucin . . . . .	1.570	Creatine . . . . .	1.20
Fatty acids . . . . .	0.177	Chlorides as NaCl . . . .	0.58
Lecithin, $H_2PO_4$ . . . .	30.800	Calcium . . . . .	6.70

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## THE CARDIOVASCULAR COMPLICATIONS OF KYPHOSCOLIOSIS WITH REPORT OF A CASE OF PAROXYSMAL AURICULAR FIBRILLATION IN A PATIENT WITH SEVERE SCOLIOSIS.

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THE functional disturbances of the circulation and of respiration, which are associated with kyphoscoliosis, do not receive the attention which they merit, in spite of the fact that they have been studied by many authors. I wish to review briefly the important literature on the subject and to present a rather unique case which affords a number of interesting problems.



Hippocrates<sup>1</sup> recognized that dyspnea is a common finding in these patients. In his chapter on the articulations he says, "and in those cases where the gibbosity is above the diaphragm, they become affected with difficulty in breathing. And yet many of them have borne the affection well and have enjoyed good health until old age, more especially those persons whose body is inclined to be plump and fat; a few of them have lived to beyond sixty years of age, but the most of them are more short-lived."

**PATHOLOGY.** Two famous clinicians of the 18th century, de Sauvages<sup>2</sup> and Cullen,<sup>3</sup> mention gibbosity as one of the causes of dyspnea. Bouvier,<sup>4</sup> however, was apparently the first to seek a rational explanation of this phenomenon. In a publication in 1858, he notes that patients with kyphoscoliosis are subject not only to dyspnea but to attacks of asthma, stubborn coughs, palpitation, cardiac arrhythmia and a tendency to syncope, and makes the significant observation that death is usually due to cardiac failure. Sixteen years later<sup>5</sup> in another review of the subject, he states that dilatation of the right chambers of the heart is a very frequent pathological finding in scoliosis. Many years previously Corvisart<sup>6</sup> observed dilatation of the right auricle and ventricle in an autopsy of a hunchback, who had died with symptoms of cardiac dilatation. He attributed it to the increased resistance offered by the distorted bloodvessels in the chest.

Traube<sup>7</sup> was the next to find on autopsy hypertrophy and dilatation of the right ventricle in a patient with a greatly deformed chest, who, before his death, had severe dyspnea and cyanosis, swelling of the jugular veins and oliguria. Since that time further evidence of the frequency of organic heart lesions, as well as of symptoms referable to the heart, has accumulated. Thus Rieder<sup>8</sup> found hypertrophy and dilatation of the right ventricle in 29 of 35 cases autopsied on Virchow's service. Eleven cases showed a hypertrophy and dilatation of the whole heart and 5 a small atrophic heart. Four patients exhibited fatty degeneration of the heart.

Similar findings were reported by May,<sup>9</sup> Poissonier,<sup>10</sup> Barié,<sup>11</sup> Fräntzel<sup>12</sup> and more recently by Meyer.<sup>13</sup> The most complete investigation, however, is to be found in the exhaustive monograph of Bachman,<sup>14</sup> published in 1899. Bachman made an intensive study of 197 of his own cases which came to autopsy, as well as of 79, which he found recorded in the literature. Of the total of 276 cases, 247 or 89.5 per cent presented an organic lesion of the heart or pericardium, but only 13 had organic valvular defects. In 154 cases the heart was examined more carefully to determine the nature of the hypertrophy and dilatation. Of these 154 cases, 87 or 56.4 per cent had hypertrophy and dilatation of the right ventricle, 27 or 17.5 per cent of the left ventricle, and 40 or 25.9 per cent of both ventricles. Bachman also noted that displacement of the heart upward and in the opposite direction to the

scoliosis is very frequent. This cardiac displacement results not infrequently in a marked tortuous and angular deviation of the aorta, the large vessels and the inferior vena cava. The aorta usually follows the curves of the spine. Kinking of a subclavian artery may cause inequality of the pulses. The right auricle shares the dilatation of the right ventricle and at times harbors thrombi, which may result in pulmonary embolism. Of 195 deaths which Bachman studied, 116 or 59.4 per cent were due to cardiac failure; 24 were due to tuberculosis.

Romberg,<sup>15</sup> in a study of 38 patients with kyphoscoliosis, found death due to myocardial insufficiency 26 times. Ljungdahl,<sup>16</sup> in addition to the hypertrophy and dilatation of the right ventricle, observed a dilatation and moderate arteriosclerosis of the pulmonary artery in 2 cases which came to autopsy:

The mechanism by means of which these pathological lesions are brought about is easy to understand. The deformed thorax is smaller than normal in size, the diaphragm is usually high. Moreover, because of the fact that the thoracic distortion is well established before bodily growth is completed, the chest lags behind the rest of the body in development. As a result of these factors the lung volume is greatly encroached upon, with ensuing atelectasis of large pulmonary fields. The capillary bed is further lessened by the constant presence of emphysema in the non-atelectatic portions of the lung. Not infrequently a chronic bronchitis is superadded and serves to obstruct the flow of the blood to a still greater degree. As a result of the diminution of the pulmonary stream bed, the pressure in the pulmonary artery becomes elevated. This is followed in time by dilatation of the pulmonary artery, often accompanied by more or less arteriosclerosis, and by dilatation and hypertrophy of the right ventricle and right auricle.

There is still another factor which places more work upon the heart. In the normal person the negative pressure in the thorax, established by each inspiration, facilitates the flow of venous blood into the right auricle and of blood from the pulmonary capillaries into the left auricle. The elastic recoil of the lungs on expiration is a further aid in the movement of the blood from the right to the left side of the heart. In patients with kyphoscoliosis the respiratory excursions of the thorax are greatly limited and so this accessory aid to the circulation is rendered negligible.

Some authors believe that owing to the factors just mentioned, an insufficient amount of blood reaches the left ventricle and explain in this manner the occasional finding of a small left ventricle in these patients.

These obstructions of the lesser circulation eventually result in insufficiency of the right ventricle, just as a long continued peripheral hypertension brings about failure of the left ventricle. Failure of the right side of the heart is seen not infrequently in a number

of diseases which obstruct the flow of blood in the lesser circulation. Among the most common of these are pulmonary emphysema, particularly when associated with chronic bronchitis, fibroid phthisis and extensive pleural adhesions.

**SYMPTOMATOLOGY.** The usual symptoms are dyspnea, cyanosis and edema of the legs. Dyspnea commonly makes its appearance within a few years of the establishment of a well marked deformity. It is due in part to the pulmonary atelectasis and emphysema, but when it grows more pronounced myocardial insufficiency becomes the most important factor. The vital capacity of the lungs is usually greatly diminished. The patients often complain of palpitation, precordial pain and vertigo. The attacks of palpitation and pain may come in crises. The pulse not infrequently is rapid and may be irregular. Sottas<sup>17</sup> published a number of clinical histories of patients in whom the pulse rate varied from 112 to 120. In many cases reported by him and others the rhythm was very irregular but no careful description of the irregularity can be found in the literature, except in the case of one of Sotta's patients, who had many extrasystoles. One gains the impression, however, from some of the case reports that the arrhythmia was due to auricular fibrillation. As the myocardial insufficiency progresses, dyspnea, cyanosis and edema become more marked, the liver becomes enlarged, oliguria is noted, and anasarca and ascites may set in.

The physical signs are for the most part inconclusive because of the great deformity of the chest. It is almost impossible to ascertain the presence or absence of cardiac hypertrophy, and murmurs are difficult to interpret. The pulmonic second sound is usually definitely accentuated. The lungs in advanced cases show signs of congestion.

**PROGNOSIS.** The prognosis in patients with kyphoscoliosis depends in a large measure upon the reserve power of the heart. Of course, not every patient develops a cardiac lesion. They may live for years complaining of nothing but dyspnea on exertion. Once the signs of myocardial insufficiency are well established, the prognosis becomes poor. Intercurrent pulmonary infections, by adding an extra load on the laboring heart, frequently precipitate the end. Women, apparently, survive their disability longer than men. In Bachman's series of 111 men, the average age at death was forty and one-tenth years, and of 158 women, the average age at death was fifty-two years. Romberg, in a much smaller series of 15 men, found the average age at death thirty-nine and seven-tenth years, and of 11 women fifty-four and six-tenth years.

**Case Report.**—The following case was observed at the Montefiore Hospital:

The patient is an unmarried woman aged twenty-nine years, weighing 72 pounds. When she was aged nine years, her mother noticed that the right shoulder was higher than the left. The

deformity of the spine was first noted when she was aged nine years and six months. This has become slowly but progressively worse, in spite of the application of all kinds of casts and braces. No pain or other symptoms referable to the spine. For ten years the patient has had attacks of dizziness, appearing every six months. During the past year the dizziness has become worse and very frequent. The vertigo lasts about twenty-four hours and the patient has to be confined to bed. "Everything before me is blurred and the room is in a constant whirl." During the same period she has had headaches three or four times a week accompanied by nausea and vomiting. For about five years dyspnea on exertion has been apparent.

Physical examination on September 30, 1920: There is a marked scoliosis with a right dorsal and a left lumbar curve. The chest is very prominent on the right side posteriorly and is drawn in, in the left axilla to form a deep groove. There is a systolic murmur over the aortic area. The pulse is regular and of good quality, rate 110. Urine shows a faint trace of albumin and occasional hyaline casts. The Wassermann reaction in both blood and spinal fluid is negative. Blood pressure 134/80.

June 10, 1922. During her stay in the hospital this past year and a half, the patient has shown little improvement. Her weight has remained stationary and the attacks of vertigo and headache still incapacitate her at frequent intervals. On May 13, 1922, she was placed on a strict Weir Mitchell rest cure. Her progress during the first two weeks was very satisfactory. She assimilated large quantities of food and gained 5 pounds in weight. Quite suddenly, on May 31, she complained of severe palpitation and shortness of breath. A few hours later she had her supper but vomited immediately afterward and the palpitation and dyspnea became greatly aggravated. She was in great distress and felt as though death were imminent. On physical examination she appeared pale and bathed in a profuse perspiration, respirations were rapid, rate 30. The heart action was absolutely irregular, the apex rate was 160, the radial rate 120. The following day the subjective symptoms were less severe but auricular fibrillation persisted and was proven electrocardiographically. On June 2, the heart action was again regular but rapid. For a week following the attack the patient has been very nervous and has complained a good deal of palpitation. She fears the onset of another attack, which, she believes, will be fatal. The pulse rate is uniformly rapid, between 120 and 150, but can be slowed to 70 by pressure on the right eyeball. The palpitation becomes aggravated from time to time, the patient stating that her heart begins to "bang." For the first four days after the attack the patient was often cyanotic, which cyanosis at times would alternate with pallor. There has been no edema of the legs. On June 5, she had an attack of

intense vertigo, which persisted for three days and was accompanied by occasional vomiting. During the attack of vertigo, objects appeared to move from right to left. She complained of a sense of oppression in the epigastrium.

Physical examination on June 7, revealed the patient lying on her left side. She always assumes this posture when complaining of dizziness. The face is rather flushed but not cyanotic. The lungs show emphysema, except in the right chest posteriorly, where breathing is somewhat diminished. No rales are heard. The apex impulse is in the fifth interspace, 9 cm. from the mid-sternal line. The left border is 10.5 cm. from the midline at the sixth rib and 7 cm. out in the third interspace. The right border is 4 cm. from the midsternal line. A systolic murmur is heard at the aortic area and at the apex. Both are widely transmitted. The pulmonic second sound is markedly accentuated. The upper border of the liver is at the fourth rib in the midclavicular line, the edge, which is tender, is 8 cm. below the xiphoid in the midline, total length 15 cm.

The pulses are equal, regular and rapid. There is some tortuosity and thickening of the right temporal artery. The following table shows the average pulse rates for several months during her stay in the hospital.

October, 1920, 105.

March, 1921, 119.

October, 1921, 116.

March, 1922, 110.

On May 29, 1922, the pulse rate become more rapid, varying between 124 and 140, until the onset of the fibrillation. Since the restoration of normal rhythm the average pulse rate has been 141. Respirations have averaged 29. An electrocardiogram taken March 22, 1921, showed a tendency toward right ventricular preponderance with P in Lead II, increased in amplitude. Electrocardiogram on June 1, 1922, showed auricular fibrillation with a tendency to right ventricular preponderance. Electrocardiogram taken on June 16, 1922, showed definite right ventricular preponderance. The blood nitrogen, the basal metabolic rate, and the eyegrounds are normal. There has been no fever at any time during one and one-half years' stay in the hospital. A roentgen-ray of the chest gives no conclusive idea of the size of the heart because of the great distortion of the spine and ribs.

June 15, 1922. For three days the patient has felt quite comfortable. Pulse regular, rate about 110. It is difficult to determine with accuracy the cause of the circulatory disturbances in this patient. Physical examination and roentgen-ray findings are inconclusive because of the deformity of the chest. It is impossible to estimate the significance of the murmurs. The rapid pulse is apparently not dependent upon myocardial disease because it can be controlled so rapidly by vagus pressure. The

electrocardiographic finding of a right ventricular preponderance suggests that in this case, just as in most other cases reported in the literature, the right ventricle is laboring under an increased resistance. It is probable that the right auricle became greatly dilated, which paved the way for the attack of paroxysmal auricular fibrillation. The longstanding headaches and vertigo, which have been observed by other authors as well, may possibly be explained by circulatory disorders of the brain.

Among the lesions found by Bachman in his large series of autopsies are cerebral hyperemia, edema or anemia, internal hydrocephalus, pachymeningitis or leptomeningitis. He believes that any one of these pathological conditions may account for the attacks of headaches and dizziness.

**Summary.** Attention is called to the frequent visceral disturbances which accompany severe kyphoscoliosis. Hypertrophy and dilatation of the right chambers of the heart, followed by signs and symptoms of myocardial insufficiency are common sequelæ. A case is described with paroxysmal auricular fibrillation and symptoms of myocardial insufficiency.

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## ABSORPTION FROM THE URINARY BLADDER.

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IN a series of experiments performed for the purpose of discovering whether bacteria would pass through the various component portions of the urinary tract, it was necessary to perform control experiments in order to determine whether the experimental procedures had damaged the structure under observation. Phenol-sulphonephthalein was employed with the bacteria, and its elimination from the kidney observed. The results of the experiments with regard to the passage of bacteria from the urinary tract have been reported elsewhere.<sup>46, 47</sup>

The review of the work of previous investigators on absorption from the urinary tract demonstrated (1) The extensive investigations on the subject; (2) the marked contradictory results; and (3) the paucity of references to the subject in American literature. This applied particularly to absorption from the urinary bladder, and since our results were so definite on this phase of the problem, we feel justified in presenting them.

*Previous Investigations of Absorption from the Urinary Bladder.* We found it impossible to review all of the voluminous literature on the subject, but believe that the more important researches are included in our bibliography.<sup>1-70</sup>

The ancients were said to have considered the bladder as being capable of absorption, but a definite conception of such a function seems not to have developed until about the middle of the eighteenth century. Experimental observations on the subject were made as early as 1779. The first conception of the subject was a physiological one, and the bladder was believed to absorb some of the constituents of the urine and thus produce a concentration of this excretion. Difference in quantity, color, amount of solids and other qualities in urine secreted by night and by day were explained on the basis of more absorption of fluid during the night. At the beginning of the nineteenth century, a practical aspect of the question developed in the possibility of administering drugs by the bladder.

While most investigators were able to obtain evidence that absorption occurs through the bladder mucosa, others were not able to obtain positive results. Thus, two groups of investigators were formed; one claimed that there is absorption through the

bladder, and the other that the bladder mucosa is impermeable. The group obtaining negative results attempted to explain the positive results on the basis that the operative procedure, or the insertion of the catheter, traumatized the bladder mucosa, and that the trauma allowed the test substance to pass out of the bladder. This idea led to the study of absorption from a previously traumatized bladder. Practically all investigators of absorption from bladders with traumatized mucosa obtained positive results. Thus a third group was formed who claimed that normal bladders will not absorb, but bladders subjected to trauma will absorb. Each of these groups has its representative in recent literature.

Many operative procedures have been devised for preparing the bladder to test its power of absorption. The first experiments were evidently rather crude. In many instances, little or no precaution was taken to prevent the substance from coming into contact with the mucosa of other portions of the urinary tract. It also was possible that in some experiments the operative procedure damaged the blood supply to the bladder. However, in most of the experiments, such possibilities for error seem to have been eliminated. In many instances the experiments were carried out on human beings. Other investigators used animals, including guinea-pigs, rabbits, cats and dogs.

Many substances have been employed in the tests. They include distilled water, normal salt solution, dextrose, saccharose, sodium chlorid, sodium iodid, sodium ferrocyanid, sodium salicylate, mercuric chlorid, ferric chlorid, lithium chlorid, potassium iodid, potassium cyanid, potassium ferrocyanid, acetic acid, boric acid, carbolic acid, salicylic acid, hydrogamic acid, carbon monoxide, carbon dioxide, hydrogen sulphite, ether, chloroform, alcohol, chloral hydrate, strychnine, atropine, cocaine, morphine, curare, pilocarpine, eserine, veratrine, nicotine, cantharides, antipyrine, urea, uric acid, albumen, milk, bacteria, diphtheria toxin and antitoxin, and methylene blue. It is readily seen that most of these substances were employed because they exerted a definite physiological action. Certain of them were selected because they could readily be detected in the blood stream; others were chosen for various reasons; a number seem to be of very little value.

The majority of investigators obtained more or less definite evidence that the mucosa of the bladder absorbed. In many experiments it was evident that very little substance was absorbed; approximately 20 per cent of the investigators were unable to obtain evidence of absorption. A careful analysis of all the data presented failed to reveal why contradictory results were obtained. The following points, however, are pertinent with regard to this. The rapid and marked response to the test substance in some instances might have been because the substance was allowed to come in contact with the mucosa of portions of the urinary tract



other than the bladder. Some of the negative results might be due to (1) Injury to the blood supply of the bladder; (2) employment of test substances which could be detected only with difficulty, or which must be in a high concentration in order to cause definite reaction; and (3) the selective absorption by the mucosa of the bladder.

Injury to the blood supply of the bladder would prevent the normal action of the mucosa, and also prevent the entrance of the substance to be detected into the blood stream. If the bladder absorbed the substance slowly its concentration in the blood stream would be low. If the substance could be detected by its physiological activity, or otherwise in small amounts, a positive result might be obtained. If, however, large amounts of the test substance were required for detection, the amounts absorbed would be too small to give positive results. It is known that various portions of the gastrointestinal tract absorb different substances. There is no valid reason why the mucosa of the bladder might not also have a similar capacity.

Various methods have been used to traumatize the mucosa of the bladder, or to produce acute cystitis for the purpose of studying absorption. Usually cantharides, turpentine, acetic acid, or sulphuric acid, were used to produce acute inflammation of the bladder. The substances were injected into the bladder at various times before the final experiments of testing the absorption. In some investigations the urethra was blocked to produce back pressure on the bladder and thus damage it. In some instances it was claimed that the insertion of a catheter into the bladder caused enough trauma to allow absorption.

It often happens that the amount of work done on a problem represents, in inverse proportion, the actual knowledge of that subject. When the results of a series of experiments, devised to give the answer to a problem, are definite, the first published report of such results is often the last because all succeeding investigations are corroborative in character. When, however, the results are not definite and slight changes in the condition of the experiment bring about either positive or negative results, opposing groups of investigators are formed who vie with each other in devising methods and performing experiments to prove their particular answer to the problem. The problem of absorption from the urinary bladder with its accumulation of research experiments and contradictory data is a good illustration of this point. After allowing for errors in technic and methods of investigation, there is no doubt that some investigators obtained evidence of absorption from the bladder, but slight changes in method, test substances, or the physiological condition of the animal could readily have made the result of the experiment negative. This, in itself, would almost imply that the answer to the problem is not of much significance.

**Method of Experimentation.** All experiments were made on dogs maintained under constant ether anesthesia throughout the experiment. Water was administered by stomach tube three to four hours before beginning the experiment in order to insure a flow of urine. The bladder and ureters were exposed through a low median incision. Constancy with regard to the amount of

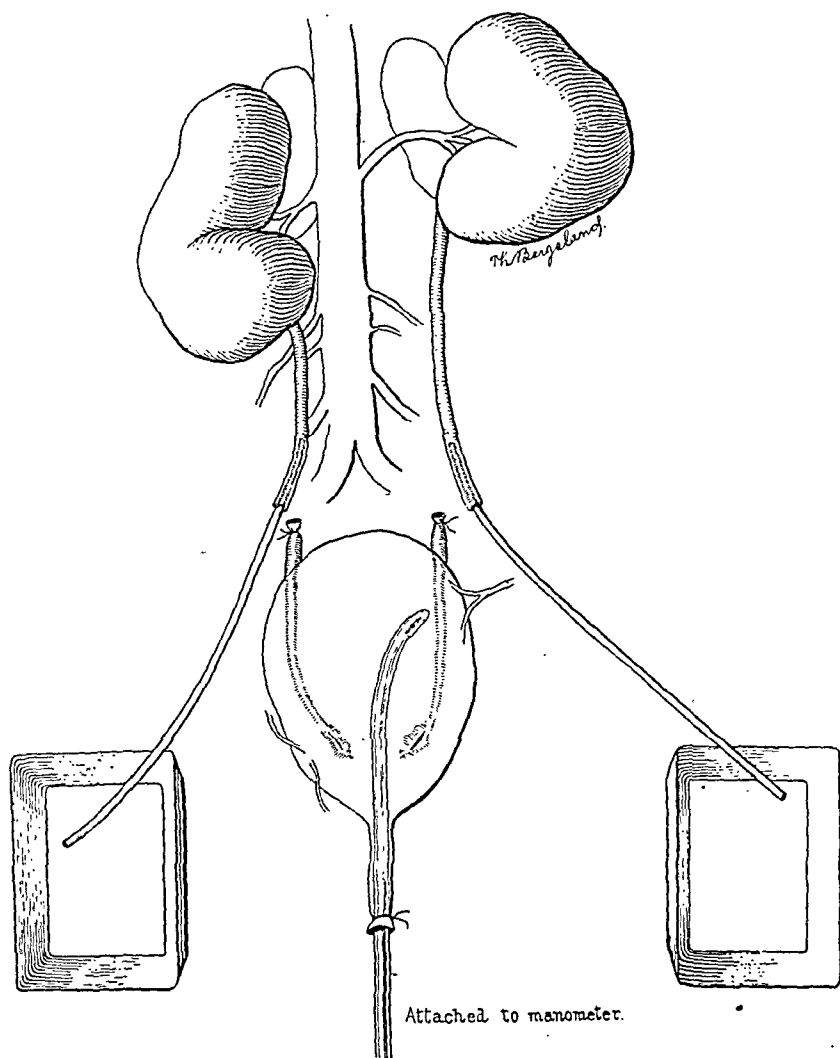


FIG. 1.—Method of introducing dyes into the urinary bladder under constant pressure.

dye in the bladder was secured by one of two methods. In one series of experiments the solution in the bladder was kept under constant pressure (Fig. 1). Both ureters were ligated and sectioned at their point of entrance into the bladder. A hard catheter was inserted into the urethra (all dogs in this series were females), and held firmly in position by a ligature placed on the bladder side

of the urethral opening. A glass T-tube was attached to the catheter. One arm of the tube was attached to a burette and the other arm to a straight glass tube about 25 cm. in length, with an internal bore of approximately 2.5 mm. and graduated markings in millimeters (Fig. 2). The dye was injected into the burette until the pressure in the bladder, as shown by the graduated tube, reached a definite point (7 to 15 cm.). In the second series of

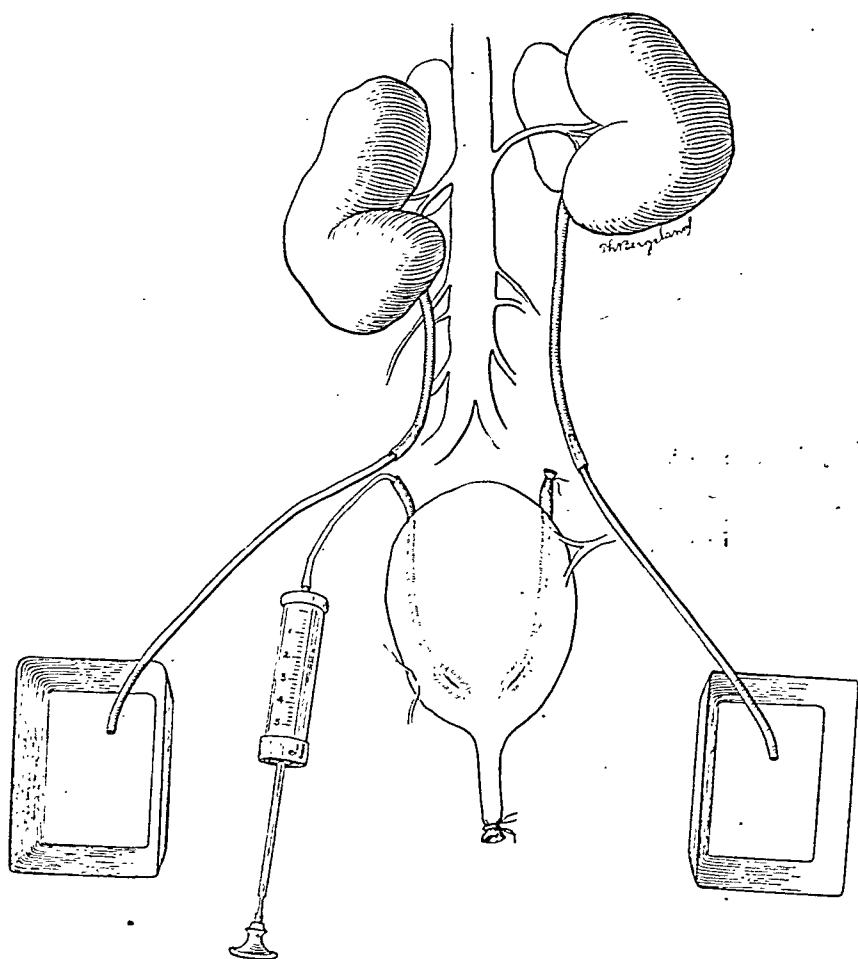


FIG. 2.—Manometer.

experiments the urethra was ligated so that the dye could not reach the urethral mucosa (Fig. 3). One ureter was ligated and sectioned at its point of entrance into the bladder; the other was ligated about 2 cm. from its point of entrance into the bladder, and the dye was injected with a syringe into the bladder by passing a hypodermic needle into the lumen of the ureter on the vesical side of the ligature. After injection the ureter was also ligated

and sectioned at its point of entrance into the bladder. An amount of dye equal to about 20 per cent of the capacity of the bladder was injected. In both series of experiments urine was collected from both ureters by a ureteral catheter. The time the dye was

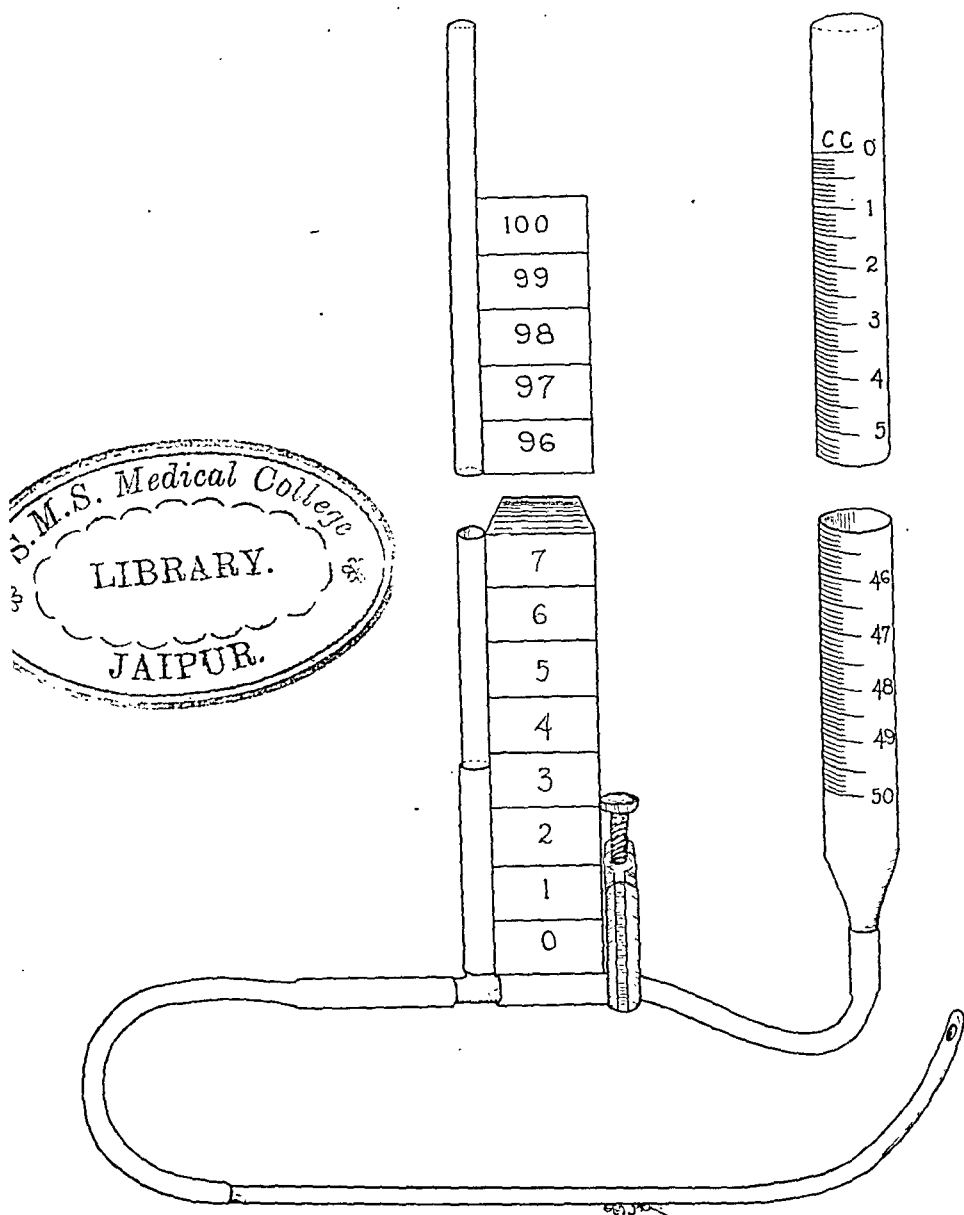


FIG. 3.—Method of introducing a given amount of dye into the urinary bladder

introduced into the bladder was accurately recorded and the urine was tested repeatedly for the dye. In some experiments indigocarmine or methylene blue was used with, or in place of, phenolsulphonephthalein.

By this technic the possibility of technical errors was avoided. The dye could only come into contact with the bladder mucosa, which was not traumatized. The bladder was only partially filled and never distended. If the dye escaped outside the bladder, it could only do so by passing through the mucosa under conditions which were physiologically possible.

TABLE I.—RESULTS OF SERIES OF EXPERIMENTS IN WHICH DYE WAS INTRODUCED INTO THE BLADDER UNDER MEASURED AND CONSTANT PRESSURE.

Experiment.	Pressure in bladder of water, cm.	Condition of bladder.	Dye used.	Appearance of dye.	Apparent amount of dye.
234	7	Acute cystitis	Phenolsulphonephthalein, 5 cc; besides 25 cc culture B. prodigiosus	26 min. after injection	Small.
236	7	Acute cystitis	Phenolsulphonephthalein, 5 cc; besides culture B. prodigiosus	None	None.
263	8	Normal	Phenolsulphonephthalein, 5 cc; besides culture B. prodigiosus	Trace from right ureter in 8 min.; from both ureters in 15 min.	Medium.
275	7	Normal	Phenolsulphonephthalein, 5 cc; besides culture B. prodigiosus	From right ureter in 50 min.; from left in 65 min.	Trace.
276	7	Normal	Phenolsulphonephthalein, 5 cc; besides culture B. prodigiosus	From left ureter in 55 min.; none from right	Small.
339	7	Normal	Phenolsulphonephthalein, indigocarmine (10 cc)	Indigocarmine from both ureters in 15 min.; trace after 1 hr. and 30 min.; sodium hydroxide added and phenolsulphonephthalein is present in urine from both ureters	Phenolsulphonephthalein large; indigocarmine large.
351	10	Normal	Indigocarmine, 10 cc; besides culture B. prodigiosus	From both ureters in 23 min.	Large.
361	7	Normal	Phenolsulphonephthalein diluted 1 to 6 with water, 5 cc	From both ureters in 16 min.	Small.
363	7	Normal	Phenolsulphonephthalein diluted 1 to 6 with water	From both ureters in 16 min.	Trace.
403	12	Normal	Phenolsulphonephthalein diluted 1 to 6 with water (13 cc)	From both ureters in 15 min.	Small amount; quantitative estimation about 1 per cent phenolsulphonephthalein excreted from both ureters in 2 hrs.
412	12	Normal	Phenolsulphonephthalein diluted 1 to 6 with water (18 cc)	From right ureter in 25 min.; none from left; left kidney found absent at necropsy	Quantitative estimation about 2 per cent phenolsulphonephthalein excreted from right ureter in 2 hrs.
421	12	Normal	Indigocarmine, 5 cc	From both ureters in 30 min.	Small.
672-20	15	Normal	Methylene blue diluted 1 to 4 with water (10 cc)	From both ureters after 2 hrs.	Trace.
673*	12	Normal	Methylene blue diluted 1 to 2 with water (27 cc)	From both ureters in 23 min.	Large.

\* Bladder filled with high pressure, then pressure lowered.

**Results of Experiments.** Nineteen experiments were performed. In three experiments we were unable to obtain evidence that the

dye had passed outside the bladder; in the other sixteen experiments the dye was detected in the urine. The time varied between the injection of dye into the bladder and its appearance in the urine. The earliest appearance of the dye was in eight minutes; in some experiments it was not detected for more than an hour; but in most instances it appeared in the urine in from fifteen to thirty minutes after its passage into the bladder. The amount of dye recovered in the urine was relatively small. In the experiments in which an attempt was made to estimate the dye excreted, only 1 to 2 per cent was obtained in two hours. The concentration of the dye in the bladder seems to be an important factor; and we used a relatively high concentration. No difference was noted between phenolsulphonephthalein and indigocarmine.

TABLE II.—RESULTS OF SERIES OF EXPERIMENTS IN WHICH A MEASURED AMOUNT OF THE DYE WAS INTRODUCED INTO THE BLADDER

Experiments.	Condition of bladder.	Dye used.	Amount of dye injected, cc.	Appearance of dye.	Apparent amount of dye.	Comments.
18	Normal	Phenolsulphonephthalein diluted 1 to 4 with water	20	From both ureters in 25 min.	Moderate	
85	Normal	Phenolsulphonephthalein diluted 1 to 3 with water	40	.....	Trace	
100	Acute cystitis	Phenolsulphonephthalein diluted 1 to 3 with water	30	From right ureter in 30 min.; from left in 60 min.	Large	
875 (1921)	Normal	Phenolsulphonephthalein diluted 1 to 4 with water	30	None	None	Injection of the dye into peritoneal cavity; no return; poor secretion of urine.
925 (1921)	Normal	Phenolsulphonephthalein diluted 1 to 4 with water	45	None	None	Poor secretion of urine; 1 cc of phenolsulphonephthalein given intravenously; no return.

In three experiments acutely inflamed bladders were produced by the application of cantharides, a few days before the beginning of the experiment. In two of these experiments the dye was detected in the urine, and in one it failed to appear.

**Discussion.** The urinary bladder is the storage reservoir of an excretion, the elimination of which is of the utmost importance. It would seem, therefore, that the mucosa of the bladder should be more or less impermeable to the passage of the normal contents of the organ. Certainly none of the waste products of metabolism which have been separated from the blood and excreted into the bladder by the kidney should be allowed to reënter the body.

Whether absorption of water which would thus increase the storage capacity of the bladder would be of any advantage is questionable.

The results of our experiments quite definitely prove that a dye can pass through the mucosa of a normal bladder. We were not able to determine whether such absorption takes place primarily through the bloodvessels or lymphatics. The total amount of dye which eventually reaches the blood stream is relatively small. The amount actually absorbed might have been greater than indicated, in view of the fact that all experiments were performed under ether anesthesia which decreases the activity of the kidneys.

The experiments indicate that undoubtedly absorption can take place from the bladder, but that the total amount absorbed is relatively small, and probably has very little practical significance.

That selective absorption of the dyes was a factor in our experiments cannot be denied, but a comparison with the results of other investigators using drugs as the test substance indicates that selective absorption is not a factor.

**Summary.** Extensive investigations on absorption from the urinary bladder present contradictory data. We performed a series of experiments using phenolsulphonephthalein as the test substance. It was found that when the dye was placed in the urinary bladder it appeared in the excreted urine. The total amount excreted was relatively small. These experiments definitely prove that absorption takes place from the urinary bladder, but only to a very limited extent. The contradictory results of previous workers were partially explained.

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## A METHOD OF ESTABLISHING DIABETIC PATIENTS ON HIGH CALORY DIETS WITH A KETOGENIC-ANTI-KETOGENIC RATIO WITHIN THE LIMITS OF SAFETY.

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WITH diabetes, perhaps more than any other disease, set rules for treatment may not be adopted; but general principles based upon a thorough knowledge of the pathological physiology of the disease, if used with critical clinical judgment, are permissible. Such general principles for diabetes have been clearly presented

by Woodyatt,<sup>1</sup> his suggestions being supported by the interesting work of Shaffer.<sup>2 3 4</sup> The discussions of these investigators on the relationship between ketogenic and antiketogenic substances of the diet which is so important in metabolism is full of suggestion for improvement in the diabetic dietary. In metabolism it is convenient to think of the ketogenic substances in terms of fatty acids, and of the antiketogenic substances in terms of glucose; and the studies of Woodyatt and Shaffer so far have shown, for practical clinical purposes, that one molecule of fatty acid is completely oxidized in the presence of one molecule of glucose. Therefore, if in a given diet, the metabolic potentialities for fatty acid do not exceed those for glucose, pathological ketogenesis should not occur. Fatty acid, or perhaps more properly speaking ketogenic potentialities, in metabolism may be derived from fat and from protein; and glucose, or antiketogenic potentialities, from carbohydrate, protein and fat. If these factors are taken into consideration in determining the diet of a diabetic patient, and the entire diet calculated and thought of as fatty acid and glucose only, new possibilities are suggested. Woodyatt<sup>1</sup> has presented formulas for calculating diets along these lines in grams, diets having the proper ketogenic-antiketogenic ratio, and which, by reason of the fat included, afford many more calories without overstepping a low glucose tolerance. The ketogenic value of a given diet is expressed by the formula:  $FA = 0.46 P + 0.9 F$ , in which  $FA$  = grams of fatty acid (or ketogenic value of the diet),  $P$  = grams of protein and  $F$  = grams of fat in the diet given.

The antiketogenic value of a given diet is expressed by the formula:  $G = 0.58 P + 0.1 F + C$ , in which  $G$  = grams of glucose (or antiketogenic value of the diet),  $P$  = grams of protein,  $F$  = grams of fat and  $C$  = grams of carbohydrate in the diet given.

The figures upon which these formulas are based are subject to revision by further work, as carefully pointed out by Woodyatt. If one is to know the ketogenic-antiketogenic ratio of food being burned by a patient, however, it is necessary to give a diet which spares his own tissues; for, if he is using his own body tissues, it is impossible to determine accurately the amount of ketogenic or antiketogenic substances being metabolized. Woodyatt, therefore, pointed out the necessity for a diet affording nitrogen equilibrium and, as far as possible, caloric maintenance. The ideal diabetic diet contains then: (1) Enough protein to maintain nitrogen equilibrium; (2) that amount of glucose which the patient has been found able to take without elevation of blood sugar; (3) fat in as large quantities as possible without having the ketogenic-antiketogenic ratio of the diet overstep the limits of safety.

In determining the amount of fat to be given so that there is one molecule of glucose in the diet for every molecule of fatty acid, cognizance is taken of the fact that the average of the molec-

ular weights of the fatty acids from all sources in the diet is 1.5 times as great as that of glucose. Therefore, a diet which contains not more than 1.5 times as many grams of ketogenic fatty acid as glucose is in the proper ketogenic-antiketogenic ratio; and we have:

Potential fatty acid from all sources in the diet,

Potential glucose from all sources in the diet = 1.5 : 1;

or,

$$\frac{\text{FA}}{\text{G}} = \frac{1.5}{1}.$$

But  $\text{FA} = 0.46 \text{ P} + 0.9 \text{ F}$ ,

and  $\text{G} = 0.58 \text{ P} + 0.1 \text{ F} + \text{C}$ .

Therefore,

$$\frac{0.46 \text{ P} + 0.9 \text{ F}}{0.58 \text{ P} + 0.1 \text{ F} + \text{C}} = \frac{1.5}{1}.$$

Solving for F (grams of fat to be given in the diet), we have  $\text{F} = 2 \text{ C} + 0.5466 \text{ P}$ , or in round figures practical for clinical purposes,  $\text{F} = 2 \text{ C} + 0.55 \text{ P}$ . By substituting in this formula the already known values for the protein and carbohydrate of the diet, the amount of fat to be given is determined.

This conception of the diabetic dietary appeared so hopeful that some months ago, due to the enthusiastic coöperation of Dr. James P. McKelvy, the study of diabetic patients along such lines was begun in the Allegheny General Hospital and the immediate results we are obtaining are very gratifying.

In thinking of the diabetic dietary along the lines suggested by Woodyatt, however, one encounters difficulty from the fact that the glucose tolerance at the beginning is an unknown quantity. To determine this factor by subtracting the amount of glucose excreted from that available to the patient from all sources, while perhaps satisfactory as a starting point, is not entirely so, because the figure arrived at is not the correct glucose tolerance of the patient in many instances. The paper of Felsher<sup>5</sup> is interesting in this connection as contributing experimental data in support of that which has been established by routine clinical observations; namely, the diabetic patient reacts as a normal person to an overstepping of the glucose tolerance by an acute, severe loss of glucose in the urine. For this reason it seemed wise to work out a method of applying the principles outlined above by which the difficulty arising from determinations of the glucose tolerance at the beginning of the study of a case of diabetes might be avoided. This has been done, and so far it has been found convenient and easy in actual practice.

In order to avoid the necessity of determining the glucose toler-

ance, it has been necessary to plan for diabetic patients during the first stages of their study on the basis of their caloric, rather than their glucose, tolerance. Thus, it is our present practice to disregard the glucose tolerance entirely in the beginning of our studies on a case of diabetes and give a test diet having three attributes, differing slightly from those presented by Woodyatt. We demand that our diets: (1) Afford nitrogen equilibrium; (2) afford caloric maintenance as nearly as possible; (3) have a ketogenic-antiketogenic ratio within the limits of safety.

In planning such a diet, two factors are known: (1) The protein to be fed—the number of grams per kilo of body weight found necessary to keep the patient in nitrogen equilibrium; (2) the total calories to be given—the number of calories calculated from the basal metabolism studies, to keep the patient on a caloric maintenance diet.

Knowing the amount of protein to be given, if the carbohydrate were known, the fat can be determined by substituting in Woodyatt's formula  $F = 2 C + 0.55 P$ . To determine the amount of carbohydrate to be given, however, a formula in addition to those already published becomes necessary. Accordingly, we have derived a formula, using the two known factors above (grams of protein and total calories the diet is to contain) which is very simple in derivation and application and has been found practicable. A table has been presented by Holmes<sup>6</sup> for the computation of diets by Woodyatt's formulas; and recently Hannon and McCann,<sup>7</sup> and O'Hara<sup>8</sup> have presented very ingenious charts, by the use of which calculations of diets according to the principles reviewed in this paper are made easy. The formula here presented is for the same purpose and, because of its extreme simplicity and immediately practical features, may also be of use to those who are working with this most interesting conception of the diabetic dietary.

The formula we use for calculating the number of grams of carbohydrate in the diet to be given when the amount of protein and total calories have been decided upon, merely records the fact that each gram of fat produces 9 calories, each gram of carbohydrate 4 calories, and each gram of protein 4 calories; therefore, the number of grams of each of these substances in the diet, multiplied by the number of calories afforded by each gram and added together equals the total caloric value of the diet. This, when expressed mathematically becomes  $9 F + 4 C + 4 P = \text{Cal.}$ , in which  $F$  = grams of fat,  $C$  = grams of carbohydrate,  $P$  = grams of protein and  $\text{Cal.}$  = total calories in the diet given. Substituting in this formula the value for  $F$  from Woodyatt,  $F = 2 C + 0.5466 P$ , we have  $9 (2 C + 0.5466 P) + 4 C + 4 P = \text{Cal.}$  Solving for  $C$  we get  $18 C + 4.92 P + 4 C + 4 P = \text{Cal.}$ , or  $22 C + 8.9 P = \text{Cal.}$ , and finally  $C = \frac{\text{Cal.} - 8.9 P}{22}$ .

The use of this formula may best be illustrated by an example: A patient weighs 70 kilos and has been found to need 1 gm. of protein per kilo of body weight to maintain nitrogen equilibrium, and 30 calories per kilo for caloric maintenance. He will, therefore, be given 70 gm. of protein in a diet affording, if he can take it, 2100 calories.

Substituting these values in formula  $9F + 4C + 4P = \text{Cal.}$ , we have  $9F + 4C + 280 = 2100$ , or  $9F + 4C = 1820$ . Substituting in this the value  $F = 2C + 0.55P$  (from Woodyatt) we have  $9(2C + 38.5) + 4C = 1820$ ,  $18C + 346.5 + 4C = 1820$ ,  $22C = 1473.5$ ,  $C = 67$ . More simply, by substituting in formula  $C = \frac{\text{Cal.} - 8.9P}{22}$ , we have  $C = \frac{2100 - 623}{22}$ , or  $C = 67$ .

By substituting the value of protein and carbohydrate determined as above outlined in Woodyatt's formula  $F = 2C + 0.55P$ , the fat to be given is found to be 172.5 gm.

The diet to be given the patient in question would then be:

	Grams.	Calories.
Protein . . . . .	70.0	280.0
Carbohydrate . . . . .	67.0	268.0
Fat . . . . .	172.5	1552.5
Total . . . . .		2100.5

Proving this diet according to the values advanced for present use by Woodyatt,  $G = C + 0.58P + 0.1F$ ,  $FA = 0.46P + 0.9F$ , we have  $G = 67 + 40.6 + 17.25 = 124.85$ ,  $FA = 32.2 + 155.25 = 187.45$ .

Glucose, or the antiketogenic value of the diet (124.85) multiplied by 1.5 = 187.28. There are, therefore, 1.5 times as many grams of fatty acid—ketogenic potentialities—as glucose—antiketogenic potentialities—in the diet. And the diet thus calculated for a patient, such as taken above, as an illustrative case meets all the specifications we demand, namely: (1) Affords nitrogen equilibrium; (2) affords caloric maintenance; (3) has a ketogenic-antiketogenic ratio within the limits of safety.

If the patient above was found unable to take 2100 calories without an elevation of blood sugar, and it was decided to try him on a diet having 1800 calories, the formula would be  $C = \frac{1800 - 623}{22}$ ; when the diet is solved for this level it would be:

	Grams.	Calories.
Protein . . . . .	70.0	280.0
Carbohydrate . . . . .	53.5	214.0
Fat . . . . .	145.5	1309.5
Total . . . . .		1803.5

This diet has glucose, or an antiketogenic value—114.7 gm.—and fatty acid, or a ketogenic value—163.2 gm.

The general plan presented above for determining diets for diabetic patients may not be followed to advantage in many cases. Often it is desirable to determine the amount of protein and number of calories to be given by factors other than those suggested. Such variation, however, does not make necessary any change in the formula above, for by substituting the values for protein and calories in the formula as it stands, the amount of carbohydrate to be given may be determined. The two diets worked out above with the same amount of protein have different caloric values. If, for any reason, one desires to change the amount of protein in the diet, while keeping the caloric value constant, the same formula may be used with equal facility for this purpose. For example, if in the first diet above affording 2100 calories it has been found desirable to give 50 gm. of protein instead of 70 gm., the formula would be  $C = \frac{2100 - 445}{22}$ ; when the diet is solved for this combination it would be:

	Grams.	Calories.
Protein . . . . .	50.0	200.0
Carbohydrate . . . . .	75.2	300.8
Fat . . . . .	177.9	1601.1
Total . . . . .		2101.9

This diet has glucose, or an antiketogenic value—122 gm.—and fatty acid, or a ketogenic value—183.1 gm.

Similarly, if in the second diet above affording 1800 calories, one desires to give 50 gm. of protein instead of 70 gm., the formula would be  $C = \frac{1800 - 445}{22}$ ; when the diet is solved for this combination it would be:

	Grams.	Calories.
Protein . . . . .	50.0	200.0
Carbohydrate . . . . .	61.6	246.4
Fat . . . . .	150.7	1356.3
Total . . . . .		1802.7

This diet has glucose, or an antiketogenic value—105.7 gm.—and fatty acid, or a ketogenic value—157.6 gm.

Even this early in the work with high-fat diets in diabetes, many considerations not touched upon in this paper have been introduced. For example, Wilder, Boothby and Beeler<sup>9</sup> have shown that the limits of safety of the ketogenic-antiketogenic ratio varies in individuals, possibly directly with the level of the metabolic rate; and Shaffer<sup>10</sup> has shown that a ratio  $\frac{FA}{G} = 3/1$  instead of 1.5/1, may in some cases be accompanied by no pathological ketogenesis. A patient who may take safely a diet with a ketogenic-antiketogenic ratio greater than 1.5 : 1 is very rare, however, and unless unusual conditions are present, such feeding is not justified.

Woodyatt<sup>11</sup> is very much in earnest in saying that diets with ketogenic-antiketogenic ratios higher than 1.5:1 should never be employed except when carefully controlled and with a full knowledge of the dangers being courted. To plan such a diet when, if ever, one feels justified in giving it, our formula, with a change in the figures, but not the principle may be used. For example, if  $\frac{FA}{G} = 3/1$ , then  $\frac{0.46 P + 0.9 F}{0.58 P + 0.1 F + C} = 3/1$  and  $F = 5 C + 2.133 P$  instead of  $F = 2 C + 0.55 P$ .

Substituting this revised value for F in the formula  $9 F + 4 C + 4 P = \text{Cal.}$ , and solving for C we get  $C = \frac{\text{Cal.} - 23.2 P}{49}$ .

In Table I appear values for F (grams of fat in diet) for different ketogenic-antiketogenic ratios, and our formula with the figures resulting by using in its derivation these different values for F.

TABLE I.

FA = Fatty acid, or ketogenic potentialities.  
 G = Glucose, or antiketogenic potentialities.  
 F = Grams of fat in diet.  
 C = Grams of carbohydrate in diet.  
 P = Grams of protein in diet.  
 Cal. = Number of calories in diet.

Ketogenic- antiketogenic ratio.	Value for F.	Formula for calculating carbohydrate in diet when amount of protein and number of calories are known.
$\frac{FA}{G} = 1/1$	$F = 1.25 C + 0.15 P$	$C = \frac{\text{Cal.} - 5.4 P}{15.3}$
$\frac{FA}{G} = 1.5/1$	$F = 2 C + 0.5466 P$	$C = \frac{\text{Cal.} - 8.9 P}{22}$
$\frac{FA}{G} = 2/1$	$F = 2.857 C + P$	$C = \frac{\text{Cal.} - 13 P}{29.7}$
$\frac{FA}{G} = 2.5/1$	$F = 3.846 C + 1.523 P$	$C = \frac{\text{Cal.} - 17.7 P}{38.6}$
$\frac{FA}{G} = 3/1$	$F = 5 C + 2.133 P$	$C = \frac{\text{Cal.} - 23.2 P}{49}$
$\frac{FA}{G} = 3.5/1$	$F = 6.364 C + 2.851 P$	$C = \frac{\text{Cal.} - 29.7 P}{61.3}$
$\frac{FA}{G} = 4/1$	$F = 8 C + 3.72 P$	$C = \frac{\text{Cal.} - 37.5 P}{76}$

Used in this manner, this simple formula makes possible the rapid and easy calculation of high calory diets with any ketogenic-antiketogenic ratio, containing any amount of protein, and afford-

ing any number of calories ever to be desired in the diabetic dietary. By its use, diets for diabetic patients, according to the principles emphasized recently by Woodyatt and Shaffer, may be calculated without knowing the glucose tolerance. And if patients are studied at first on the basis of their caloric, instead of their glucose tolerance, a method for the study of the diabetic dietary is available by which the difficulty of determining accurately the glucose tolerance early in the study of the case is avoided.

The details of application of this method of procedure have not been presented, but will appear later in a clinical report of the cases studied. It is hardly necessary to say that this, or any other suggestion, may not be employed as a routine procedure for all cases, or used blindly and unintelligently in any case. It should, perhaps, be emphasized that we present it for use only as a method of procedure in establishing diabetic patients on their maximum food combinations when they have been brought to the stage where this is in order. For this purpose it has been found convenient and practical, and has rendered much more simple the applications of the principles of diabetic feeding outlined above.

**Summary.** Following upon the recent studies of Woodyatt and Shaffer on the ketogenic-antiketogenic ratio in metabolism, and the practical application of these studies for establishing diabetic patients on a high-calory diet, a conception of the diabetic dietary, based primarily on the caloric, rather than principally upon the glucose tolerance of the patient, is presented; and a simple formula for the necessary computations is derived. This method of procedure is helpful because it enables one to study diabetic patients without first establishing the glucose tolerance, which is so difficult to determine accurately. The early results obtained by this method of feeding diabetic patients have so far been extremely gratifying.

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**MEDICAL TREATMENT OF GASTRODUODENAL ULCER,  
WITH ESPECIAL REFERENCE TO THE USE OF A  
RICE-WATER MIXTURE.\***

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MUCH has been written about gastric ulcer, or, if you please, peptic ulcer, and much has been suggested by way of treatment for this perplexing lesion. Medical measures claim a high percentage of therapeutic triumphs as a result of their practice, while the surgeon puts forth splendid statistics to show the efficacy of his scalpel. Each of these opposing camps claims failures on the part of the other. The medical man points to the surgical derelicts he has had to care for and the surgeon calls attention to the innumerable times he is called upon to rescue the medically treated patient or perhaps, what is more to the point, his doctor. The literature is filled with many suggestions for the non-surgical care of these cases, while an almost equal amount of space is devoted to the best non-medical technic to follow. The treatment of gastroduodenal ulcers is, in other words, not universally satisfactory.

When a multiplicity of suggestions are made for the relief of any disease, ordinarily none of the methods are actually effectual. This does not seem to be true of ulcer cures, for the relationship of cause and effect is usually in this connection a clear-cut one. Sometimes uncertain etiology makes for a varied therapeutics. This too does not seem to be the case here, even though the cause of ulcer is not certainly settled. Obviously many methods of handling ulcers medically or surgically are recommended because of the many changing indications to be met with in these cases. For example, the problem of the chronic cicatrized ulcer is quite apart from that of the earlier gastric lesions and, therefore, must require different care.

Lack of success in the treatment of gastroduodenal ulcer is dependent for the most part upon a failure to appreciate these changing therapeutic indications. Variable results are reported when the same method of treatment is applied in all cases; failures would of necessity follow such a practice. Often, of course, conditions do not permit thorough application of the indicated treatment in a given patient, a circumstance which does not allow for a uniformly successful outcome. Sometimes, in the interests of time economy, surgery is practised when a right sort of medical regimen would have done better. On the other hand, quite fre-

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quently a medical cure is quite impossible in the presence of very advanced pathology. Surgery promises quick results, but a careful analysis shows that this speed is more apparent than real. The post-surgical ulcer case requires, as a rule, a long period of good medical care if lasting effects are to be accomplished. Here, as elsewhere, a big opportunity for practice, with attention to early diagnostic and therapeutic detail, makes for successful results, while inexperience and short cuts often spell failure. Almost every one has some particular treatment with which he is especially familiar. Every method of handling ulcers therefore has its champions and critics.

All suggested medical treatments require time, and are usually complicated, necessitating much thought and detailed attention. Casual practice of this method is therefore doomed to meet with many ulcer failures. Rest of the mind and body, but more particularly of the stomach, is a part of medical treatments in general. Bed rest and preliminary degrees of starvation are usually suggested with provisions made for enematization or the introduction of fluids into the body by hypodermoclysis. The suggested diets generally provide for small fractional feedings of bland, non-irritating food at frequent intervals. Medical men are more or less divided as to whether or not the diet should be purely carbohydrate or protein. Some few combine both types of foods. The list includes milk, eggs, broths, gruels, starch solutions and other articles too numerous to mention. The carbohydrate enthusiasts feel that proteins, instead of diminishing, stimulate an overproduction of gastric juice, while the proponents of the latter diet contend that it serves to combine with the free acid and thereby minimizes its digestive action upon the ulcer. The fact of the matter is that the use of both diets is followed by successes and failures. At times this, and at times another diet or scheme succeeds. Sometimes a medical treatment should not even be attempted. Feedings by transduodenal intubation often yield gratifying results. It is part of all treatments to first of all seek out infective foci in the body and then attempt to erase them. The relationship of ulcer to focal infection is now upon quite certain ground. Medicines used in conjunction with diets usually aim to influence hyperfunctionation of the stomach whether this be of motility, secretion, or sensation. They are chiefly concerned in the neutralization of the free acid. Other medication is often employed to reduce gastric irritability. In this way nerve sedatives and antispasmodics play an important role in many medical treatments. Drugs must also be employed quite frequently to hurry the intestinal transportation of the unusually non-stimulating and scanty food residue. Hydro-mechano-electrotherapeutic procedures occupy a large place in most of the ulcer regimens.

Granting that the case is not accompanied by high-grade cicatrized pyloric obstruction, that there is no perforation or that carcinomatous implantation is not a reasonable possibility, that there is no perigastric abscess or hour-glass contraction, and that there are no unusual perigastric adhesions, then variously suggested medical treatments can be tried. All of them, however, usually emphasize hospitalization or at least bed treatment. Most textbooks and literature in general devote much space to a strict rest treatment of ulcer with an occasional reference to the possibilities of ambulatory treatment. Sometimes the patient's social or financial status will not permit bed treatment, to say nothing of hospital care. Sometimes the patient's mental attitude is contradictory to this mode of treatment. At times surgical treatment is not acceptable to the ulcer victim, and at other times the surgeon may suggest a preliminary trial of medical measures. What can be tried in these events? What are the therapeutic possibilities in the patient coming to the out-patient department? Surely these cannot be thrust aside untreated.

All of the well-known treatments can be applied with certain modifications to the average ambulatory case. Hourly feedings can be arranged for with little difficulty. Usually thirteen a day are suggested, but sometimes two-hour intervals serve equally well. Women working at home can of course easily provide themselves with the necessary diet, while the working man or working woman can carry enough food in thermos bottles or the ordinary magnesium citrate bottles. Many cases can be started on a milk and cream combination after the Sippy method, using of course adequate amounts of calcium carbonate, bicarbonate of soda and magnesium oxide between feedings. If the patient tends toward constipation the amount of magnesium oxide taken is increased, while the looseness of the bowels is a signal for an increased intake of calcium carbonate or even the addition of bismuth subcarbonate. Lime water or sodium citrate, 0.6 gm. may be added to each one of these milk and cream feedings. Sodium citrate seems to lessen the irritability of the milk curd. At night or at some time out of working hours, hot-water bags, ice bags, poultices, or tincture of iodine may be applied to the epigastrium for varying periods of time. The gastric retention cases can be trained to empty their stomachs at night with the stomach or, better still, the duodenal tube.

There are always a number of cases in whom the milk and cream regimen does not promptly arrest pain or other symptoms. In these cases we have found a rice-water mixture used by Dr. Joseph Sailer, of Philadelphia, to be of very great value. In our out-patient department<sup>1</sup> a patient is given a printed slip of paper con-

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taining the following information and suggestions with supplementary explanations by the dietitian:

### RICE-WATER FORMULA.

Boil one-half cup of rice in five cups of slightly salted water until soft. Strain off and cool one quart of the water. When cool add to it four tablespoons of lactose, whites of four eggs, slightly beaten, and one-half cup of cream. Keep the mixture in a cool place.

Take \_\_\_\_\_ of the mixture every hour throughout the day, until thirteen feedings have been taken.

Secure a bowel movement each day. If necessary use milk of magnesia for this purpose.

Take note of weight and report back after \_\_\_\_\_ days. Lactose is milk-sugar and may be purchased at any drug store.

The palatability of the rice-water mixture may be influenced by the addition of peppermint, chocolate, nutmeg, or coffee. It is a difficult matter to accurately determine the caloric value of this mixture, but it is quite likely that a quart will yield at least 750 calories. Two to six-ounce portions of this preparation are usually taken at hourly intervals for thirteen feedings per day. There are, of course, cases who are advised to take the mixture at two-hour or even longer intervals. After the symptoms are allayed for twenty-four hours at least, the caloric value of the rice-water mixture is increased by adding more cream, sugar or whites of eggs. Very quickly after this the patient goes on to either a partial or entire milk and cream mixture and, if well tolerated, passes on to a soft or light diet, usually preponderant carbohydrate.

In addition to the mixture we frequently employ some one of the antacid preparations. Another favorite procedure is to prescribe after the first, seventh and thirteenth feedings and at bedtime a teaspoonful of the popular nux, soda and gentian mixture of our hospitals. To this prescription we may add sodium bromide 0.3 to 0.6 gm., and sometimes, if required, a variable amount of the fluid extract of *rhamnus purshiana*.

It is most gratifying to note the rapidity with which symptoms disappear when this mixture is prescribed. Many patients are given this diet in a tentative way while in the course of study. Frequently nothing else is required. The neurosis cases, with the exception of the aërophagics, do especially well under this regimen, when quite frequently they object to other milk mixtures. In the functional cases we sometimes use a powder containing 0.3 gm. each of sodium bromide, carbolignum, calcium carbonate and magnesium oxide. All patients are impressed with the fact

that strict adherence to instructions is required for success. They are reminded that successful gastric therapeutics means months and sometimes years of attention to self-care and self-control in matters of diet. They are also impressed with the necessity of securing a bowel movement each day. They are advised to observe their weight and report back if there is much loss in this direction. Of course, every effort is made to maintain the patient's weight, usually by increasing the caloric value of the mixture.

If the history, physical examination, test-meal and roentgen-ray studies point to an ulcer diagnosis, this rice-water treatment seldom fails to relieve symptomatically, and in time we believe pathologically. The use of this mixture has now been observed over a period of time and in a sufficient number of cases of varying types to enable one to say that it meets most satisfactorily the problem of the gastric irritability syndrome both without and, more especially, with ulcer. If it fails to relieve we have usually found our diagnosis to be incorrect or that we are dealing with a case indicating surgery.

We have even observed twenty-four-hour pyloric obstruction cases return to almost normal gastric motility in several weeks on this rice-water ambulatory regimen; of course, this, too, has been our experience with the Sippy method as well. The subperforation or adhesion cases do not yield very readily to any medical treatment. The type adherent to the pancreas have been especially difficult to deal with. Even the surgeon is content with only a gastrojejunostomy in these patients. In patients who have not had roentgen-ray studies, failure of the rice-water mixture to relieve symptoms strongly indicates the use of this diagnostic measure. Very occasionally the rice-water mixture succeeds in a bed treatment when it has failed in ambulatory treatment. Its best results are obtained in the cases accurately diagnosed in early stages. Early diagnosis is just as desirable here as in other fields of medical endeavor. The rice-water mixture is easily prepared and kept. Many patients obtain such great relief that it is difficult to persuade them to go on to more complex food.

**Summary.** 1. Attention is called to some reasons why variable results are reported in gastroduodenal ulcer treatment.

2. Reasons for therapeutic failures are noted.

3. The general plan of medical treatments is reviewed.

4. The possibility of ambulatory treatment in peptic ulcer is reemphasized with some directions for cases in whom it is the only alternative.

5. The satisfactory use of a rice-water mixture in the gastric hypersyndrome, more especially with ulcer, is suggested.

6. Claim is made for this mixture that, although it adds another diet to the already crowded field of ulcer therapeutics, in our experience, it has tended more to simplify than complicate the problem of treating gastric irritability.

## THE STABILITY OF ADRENALIN HYDROCHLORIDE IN VARIOUS SOLUTIONS.

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THE active principle of the medullary portion of the suprarenal glands, properly designated as epinephrin, has become so widely known under its trade name, that it will be referred to as adrenalin in the present article.

Before the active principle of the suprarenals had been isolated in pure form and its formula determined, it was recognized that it was readily destroyed by oxidizing agents. It was learned, moreover, that this oxidizing action was accelerated by an alkaline reaction, while it was prevented, or markedly retarded, by even a slight degree of acidity. The lability of the substance is appreciated by the manufacturers of adrenalin who state on the labels of the bottles that chloretone and carbonic acid are added in order to prevent deterioration. They also point out that simple dilution in salt solution gives rise to a rapid loss in pressor action of adrenalin. They have not emphasized, however, that the addition of alkalis is apt to hasten deterioration; and we have found that local physicians who prescribe adrenalin for its constrictor action in the nose and throat are apparently unaware that this desired action may fail to be elicited because of the nature of the vehicle in which the drug is exhibited.

Investigation in the dispensary of the Medical College of Virginia has shown that the following vehicles are frequently used in conjunction with adrenalin: Glycothymoline; borolyptol; alkaline antiseptic solution, N.F.; Dobell's solution; listerine; and normal saline. It was decided, therefore, to ascertain the keeping qualities of adrenalin in these various solutions.

Solutions of adrenalin were prepared, in the strength of 1 to 100,000, in each of the preceding diluents. The pressor action of these solutions was determined at the time they were made up by ascertaining the effect they were capable of producing on the blood-pressure of a dog. The animals used in these experiments were either anesthetized by the intracerebral injection of magnesium chloride, or they were decerebrated. In all instances the vagi were cut in the neck to avoid the inhibitory action of adrenalin on the heart, and artificial respiration was employed. The injections were made into the femoral vein and the carotid blood-pressure

was recorded by a mercury manometer. The dose selected was 0.5 cc of the 1 to 100,000 solution per kilogram of body weight.

Since the circulatory effects of adrenalin under the conditions described are evanescent, it was possible to compare the relative strength of a number of different preparations on any one dog. In order, however, to obtain information as to the keeping qualities of the solution, it was necessary, obviously, to make use of a number of different animals on succeeding days. In carrying out these later experiments, in addition to comparing the different solutions with each other, their pressor action had to be compared with that of a standard prepared by diluting a small amount of the stock solution in physiological saline.

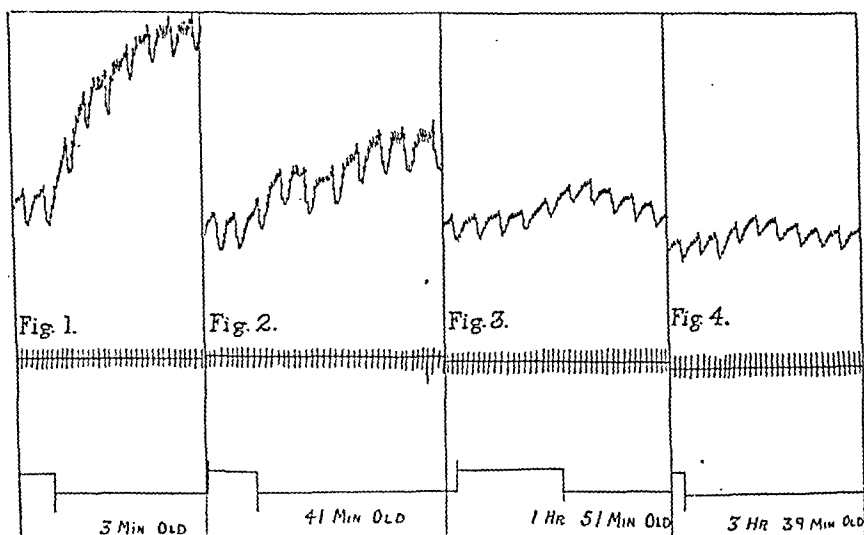


CHART I.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kg. in borolyptol. Fig. 1, three minutes old; Fig. 2, forty-one minutes old; Fig. 3, one hour and fifty-one minutes old; Fig. 4, three hours and thirty-nine minutes old.

The results of these experiments were surprising in indicating how rapidly adrenalin was destroyed in certain of the commonly used vehicles. Thus, the dilution in borolyptol was found to be practically devoid of any pressor action at the end of a little over three hours and a half. The tracings in Chart I, all obtained from the same dog, illustrate in a striking manner the progressive and rapid loss of strength of the adrenalin in this vehicle. The stability of adrenalin in glycothymoline is only slightly greater than it is in borolyptol. Thus, at the end of three hours and forty-one minutes there had been a decided loss in activity, while twenty-four hours later there was no evidence of any constrictor action (Chart II). In Dobell's solution there was a distinct loss of activity at the end of twenty-four hours (Chart III) and the preparation was found to be inert at the end of a week. Since

these three vehicles are all alkaline in reaction, a destruction of adrenalin is to be expected when it is dissolved in one of them. It is evident that the addition of adrenalin to borolyptol or glyco-

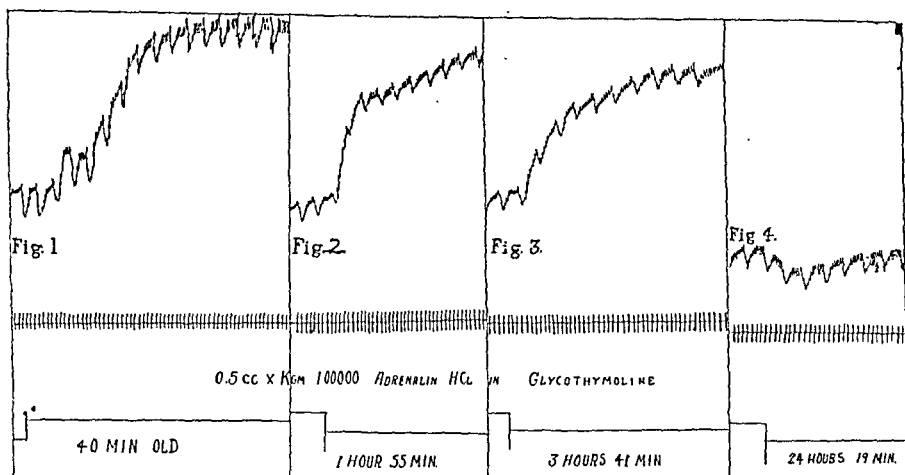


CHART II.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kg. in glycothymoline. Fig. 1, forty minutes old; Fig. 2, one hour and fifty-five minutes old; Fig. 3, three hours and forty-one minutes old; Fig. 4, twenty-four hours and nineteen minutes old.

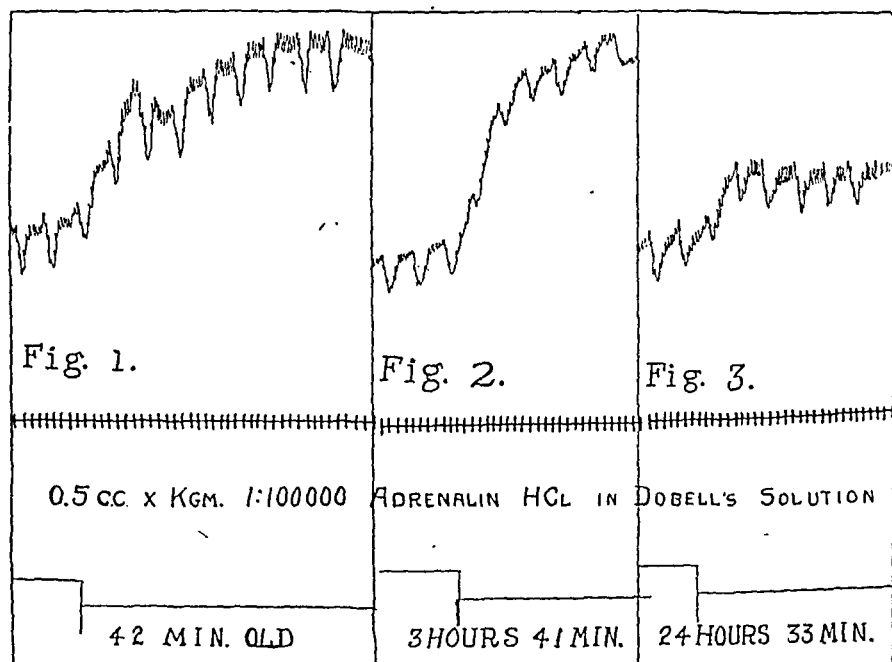


CHART III.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kilogram in Dobell's solution Fig. 1, forty-two minutes old; Fig. 2, three hours and forty-one minutes old; Fig. 3, twenty-four hours and thirty-three minutes old.

thymoline is practically useless, so rapid is the oxidation of the amine. Even in Dobell's solution one could expect no constrictor action from the adrenalin at the end of a week.



Williams and Sweet have recently called attention to the fact that the reaction of physiological salt solution is not necessarily neutral and constant. They showed that such solutions gradually tend to become somewhat acid from absorption of the carbonic acid of the air. In our experiments with saline we found that adrenalin in a dilution of 1 to 100,000 in 0.9 per cent sodium chloride was more stable than in the three vehicles first discussed. After

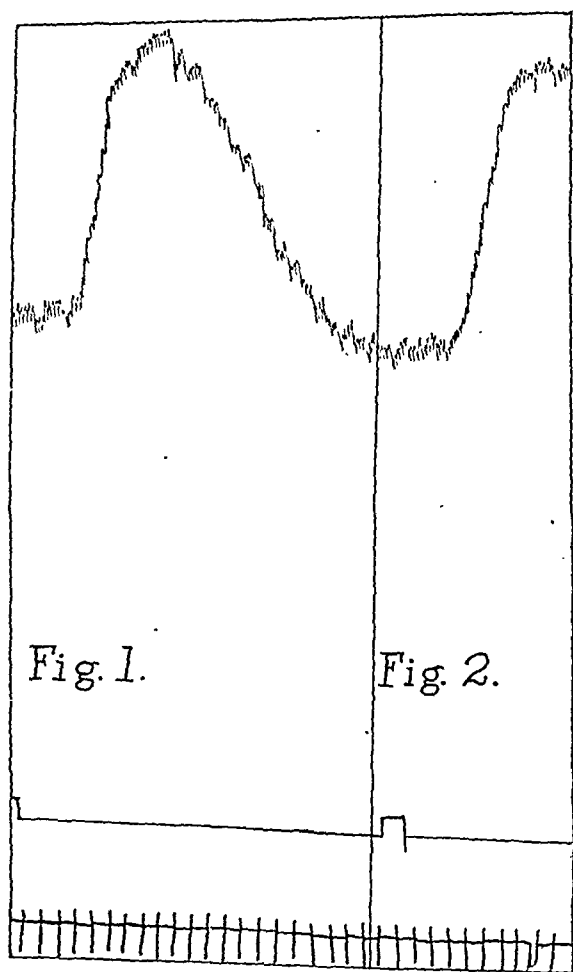


CHART IV.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kg. Fig. 1, in fresh saline solution; Fig. 2, in listerine, nineteen days old.

a month there was little or no loss of pressor action and it became inert only after fifty-nine days. We were possibly in error in assuming that our salt solution was neutral, as no determination of its hydrogen-ion concentration was made. Such results with saline cannot be widely applied because, as has been explained, various specimens of saline may behave differently, and it is quite possible that the one with which we have been experimenting had

acquired a certain degree of acidity. Incidentally, it should be noted that the addition of small amounts of antipyrine to adrenalin in salt solution causes a relatively rapid loss of pressor action to the solution.

Listerine and the plain antiseptic solution of the N.F. are both slightly acid in reaction, due to their content of benzoic acid and boric acid respectively. Our early experiments indicated that the

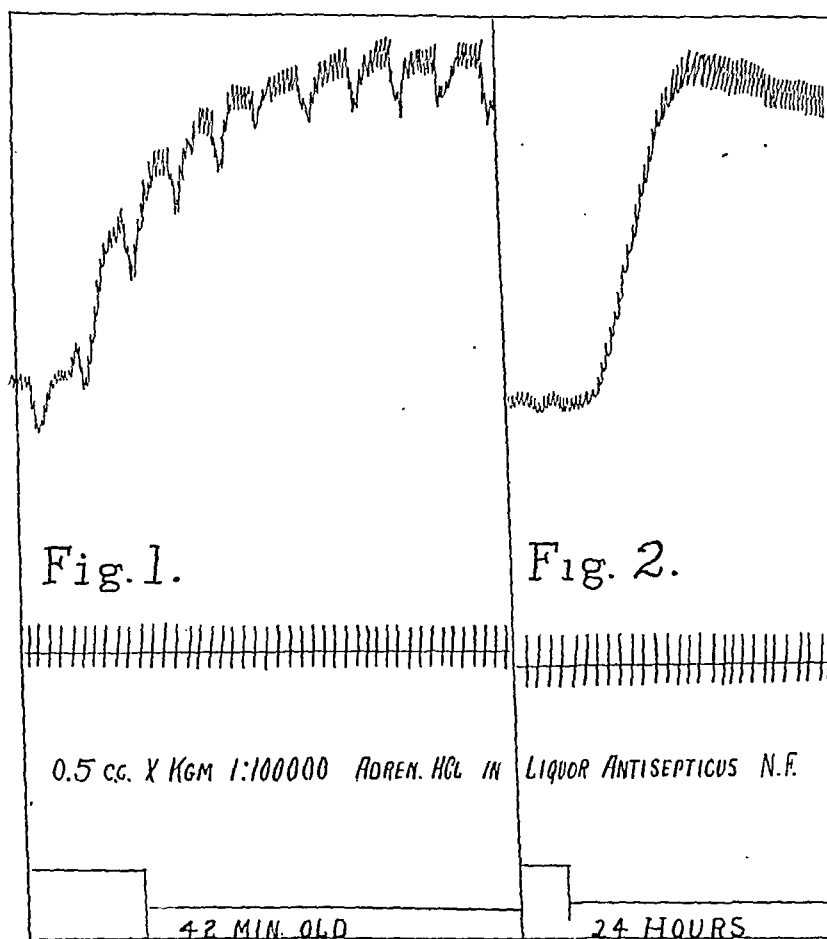


CHART V.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kg. in plain liquor antisepticus, N. F. Fig. 1, forty-two minutes old; Fig. 2, twenty-four hours old.

solutions of adrenalin in these vehicles preserved the pressor action remarkably well. Thus it was found that adrenalin in listerine was fully as active as the freshly prepared standard at the end of nineteen days (Chart IV). The solution of adrenalin in the plain antiseptic solution, N.F., was similarly stable (Chart V), and we have found no appreciable loss of strength at the end of four months.

The next step was to determine whether the benzoic acid present in listerine is, of itself, sufficient to manifest this preservative

action. Accordingly, solutions of adrenalin were made up in the strength of 1 to 100,000 in both 0.2 per cent and 0.02 per cent benzoic acid. The subsequent testing of these solutions revealed that the

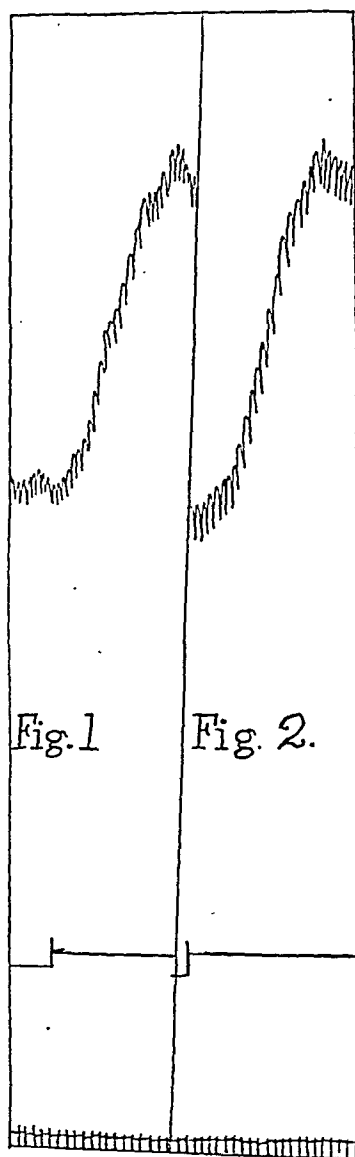


CHART VI.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kg. Fig. 1, fresh saline solution (standard); Fig. 2, benzoic acid, 0.02 per cent, nineteen days old.

benzoic acid was quite effective, there being no evidence of loss of pressor activity at the end of nineteen days, even in the weaker concentration (Chart VI). In the strength of 0.2 per cent benzoic acid the solution was very stable, losing only about 15 per cent of

its constrictor action in fifteen months. Even in the strength of 0.02 per cent benzoic acid, about 33 per cent of the pressor action was manifest at the end of fourteen months (Chart VII).

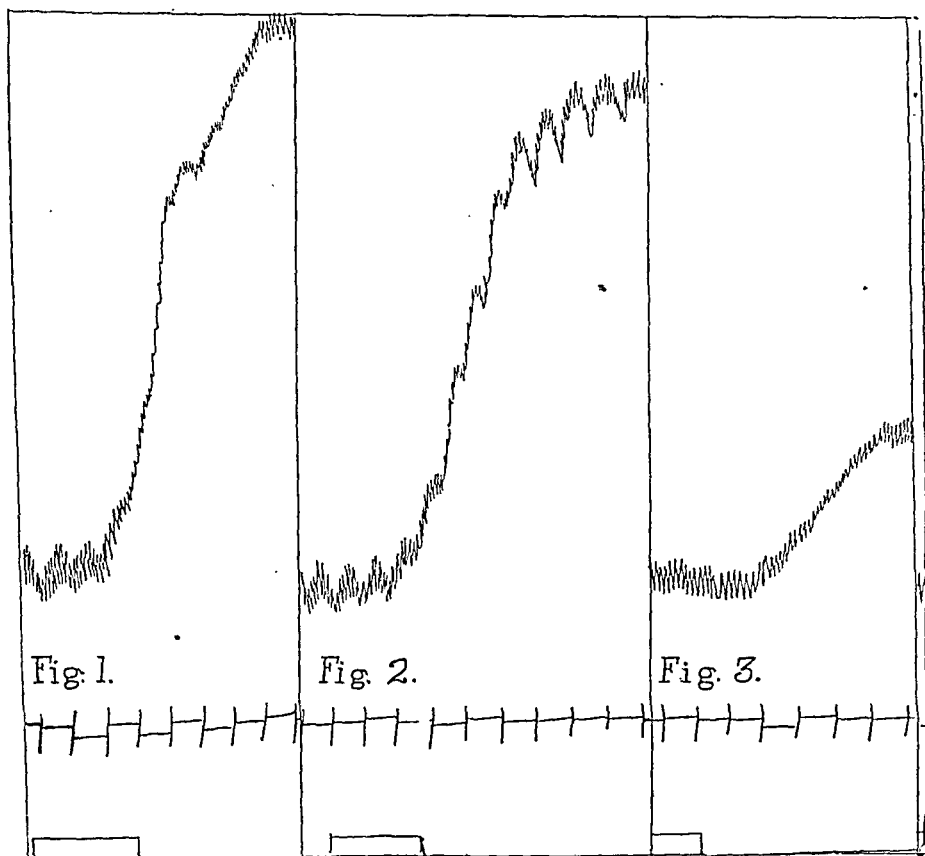


CHART VII.—Adrenalin hydrochloride 1 to 100,000; 0.5 cc per kilogram. Fig. 1, fresh saline solution (standard); Fig. 2, benzoic acid, 0.2 per cent, fifteen months old; Fig. 3, benzoic acid, 0.02 per cent, fourteen months old.

**Conclusions.** As a result of the above experiments we would suggest that adrenalin may be prescribed in normal saline in cases where prompt utilization is intended. If, however, the pressor activity of the adrenalin is to be preserved for any length of time, we would recommend its dilution in a weak solution of benzoic acid. Whether the demonstrable stability of adrenalin in such a solution is due to some action of the benzoic acid *per se*, or due simply to the hydrogen-ion concentration of the solution, we are not prepared to say, but we are now engaged on further experiments to determine this point. Our investigations demonstrate graphically the utter uselessness of prescribing adrenalin in solutions which have an alkaline reaction.

## REVIEWS.

I BELIEVE IN GOD AND IN EVOLUTION. By WILLIAM W. KEEN, M.D., Emeritus Professor of Surgery, Jefferson Medical College, Philadelphia. Pp. 100; 3 illustrations. Philadelphia: J. B. Lippincott Company, 1922.

HERE is the credo of a great man simply stated for any who care to read sympathetically. The author is distressed that others cannot see the unity of the divine plan as clearly as he does. He believes in God and in evolution and this little book evidently has been written in the hope that by restating the matter in almost primer language some, who now see the theory of evolution and the Christian religion as antagonistic, may be brought to the opposite view. There is nothing controversial in the book, there is nothing so scientific as not to be understood by any reader. It is a book rather for one who, untrained in science and ignorant of the facts upon which the theory of evolution is founded, yet believes in Christianity. It cannot fail to carry a convincing message to all whose minds are other than closed. P.

WHAT TO EAT IN HEALTH AND DISEASE. By BENJAMIN HARROW, PH.D., College of Physicians and Surgeons, Columbia University. Pp. 195; 17 illustrations. New York: E. P. Dutton & Co., 1923.

THIS book, by the author of "Vitamines, Essential Food Factors," etc., is, as the preface states, a guide for those who want to know what to eat and why. Written for popular use, it puts a scientific knowledge of foods into everyday language, with quotations from the sources, and references for further study. There are chapters, among others, on the planning of meals, the nursing mother, infant feeding, vegetarianism, overweight and underweight, constipation, etc. The relationship of diseases and diet is clearly set forth, and there is a final chapter on the chemistry, physiology and anatomy of the digestive tube. For the patient who wishes to follow intelligently the directions of his physician, this will prove a very helpful book. McC.

RADIUM BIBLIOGRAPHY AND ABSTRACTS OF SELECTED ARTICLES ON RADIUM AND RADIUM THERAPY. Compiled by American Institute of Medicine for United States Radium Corporation, New York. Pp. 132 and 164. New York: 1922.

THE bibliographical pamphlet presents in 15 sections several thousand references on the use of radium and results obtained from its discovery up to January, 1922. In each section the titles are arranged by year of appearance, the most recent years appearing first. This collection should prove a useful addition to a working library, although it is far from complete, especially in non-clinical lines. The literature before 1903, is particularly meager and one misses the pioneer articles of Becquerel and the Curies. The pamphlet of abstracts is even more restricted, but will doubtless be welcomed by radiotherapeutists. K.

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HANDBOOK OF ELECTROTHERAPY. By BURTON BAKER GROVER, M.D.; President of the Western Electrotherapeutic Association; Member of the Radiological Society of North America, etc. First edition. Pp. 420; illustrated with 103 engravings in the text and 6 plates of 12 charts. Philadelphia: F. A. Davis Company.

THE last few years have witnessed a number of new volumes written on this same subject of electrotherapy. The book covered by this review discusses very completely all phases of the subject beginning with the fundamental principles of electricity. Chapters are included on high blood-pressure, hyperpiesis, genito-urinary diseases and a whole host of other conditions said to be amenable to electrotherapeutic procedure.

The style is exceedingly simple. It would seem that the author in his endeavor to achieve simplicity of style has often sacrificed accuracy of statement from the clinical standpoint. From the electrotherapeutic side, Grover is naturally hyperenthusiastic, just as all are who are engaged in this work. There is, of course, a group of medical men who are too skeptical concerning the efficacy of this branch of therapeutics. The middle ground seems a more tenable one, namely, that there are many functional conditions which are very favorably influenced by electricity and indeed there are some organic lesions in which therapy of this sort seems to make the patient more comfortable.

One would prefer to read less of Abrams and his methods. A suggested addition to the value of such a book would be the inclusion of statistical records with accurate follow-ups of a large series of cases treated by electrotherapeutic measures. If such statistics,

honestly made, would show that electricity uniformly does influence favorably all the diseases covered in this volume, then we would be in accord with the spirit of the author. The writer in the preface justly calls attention to the fact that little opportunity is given to medical men as undergraduates to become familiar with modern methods of electrotherapeutic application. It does seem fair to say that our medical schools should emphasize this branch more than they are in the habit of doing. It is quite possible that there would be more converts to this field as a result of more successful results and that there would be fewer practitioners of the various cults. S.

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**STUDIES IN THE STANDARDIZATION OF THE WASSERMANN REACTION WITH THE DESCRIPTION OF A NEW METHOD.** By JOHN A. KOLMER, M.D., Professor of Pathology and Bacteriology in the Graduate School of Medicine of the University of Pennsylvania, and Head of the Department of Pathology in the Research Institute of Cutaneous Medicine of Philadelphia; assisted by C. P. BROWN, T. MATSUNAMI, A. M. FLICK, A. RULE, M. E. TRIST, and E. YAGLE. Pp. 580; 7 illustrations. Philadelphia: 1923.

IN this volume the reprints of one publication appearing in the AMERICAN JOURNAL OF MEDICAL SCIENCES, and those of thirty-two publications appearing in the American Journal of Syphilis during the years 1919 to 1922 are collected. These publications represent an extensive experimental investigation of the values of the more plausible of the many technical modifications suggested in antecedent literature on the technic of the Wassermann test. The modifications shown to be of greatest worth are utilized in building a method for the conduct of the test. S.

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**TEXT-BOOK OF PEDIATRICS.** Edited by Prof. E. FEER, Director of the University Children's Clinic, Zurich; translated and edited by JULIUS PARKER SEDGWICK, B.S., M.D., Professor of Pediatrics, University of Minnesota, Medical School; and KARL ABRENDT SCHERER, M.D., F.A.C.P. Pp. 917; 262 illustrations. Philadelphia and London: J. B. Lippincott Company, 1922.

SEVENTEEN American pediatricians have translated the seventh edition of the author's well-known book on pediatrics. The character of the work performed by the American collaborators is of a very high order, and additions have been made both to

text and illustrations. No attempt has been made to describe in detail diseases discussed at length in the general text-books on medicine, but measles, pertussis, varicella, and nutritional disturbances are dealt with in especial detail. The book is up to date, and can be recommended without hesitation to the general physician as well as to the pediatrician. A.

AN INDEX OF PROGNOSIS AND END-RESULTS OF TREATMENT. By VARIOUS AUTHORS. Third edition. Pp. 594. - New York: William Wood & Co., 1922.

As our treatment of various diseases improves, the prognosis becomes more favorable; therefore, constant revision of any work on prognosis is required. The present volume reflects the better prognosis offered by the more modern methods of treatment of epithelioma of the lip, strangulated hernia, and intussusception. The sections on venereal diseases, gynecology, and obstetrics have also been rewritten, and a new section on ophthalmology has been contributed.

Those who desire to find a brief discussion of medical and surgical diseases, with special reference to prognosis, will be pleased with the book; however, the work will still be a disappointment to those who are awaiting a scientific statistical study of the probability of death or disability, and the expectancy of life in each disease. A.

IMPOTENCY, STERILITY, AND ARTIFICIAL IMPREGNATION. By FRANK P. DAVIS, PH.B., M.D. Second edition. Pp. 163. St. Louis: V. C. Mosby Company, 1923.

A CAREFUL reading of this book has failed to convince the reviewer of its value as an addition to his library. The first one hundred and ten pages are a hazy, Freudian discussion of such topics as sensuality in women, the effect of odors on internal secretions, and the influence of the senses of smell, sight and hearing in impotency.

The directions for treatment of sterility and impotence include suggesting that the woman sing at the top of her voice during the copulative act as a sure remedy for sterility, and that Chinese incense burned in the room gives off an odor that excites sexual power and desire.

The author loans sterile couples a speculum and a syringe in order that they may practice artificial impregnation at their convenience. Such a proceeding may be questioned. It is difficult to understand the necessity for this second edition. W.



STERILITY IN WOMAN; ITS CAUSES AND TREATMENT. By ROBERT A. GIBBONS, M.D., M.R.C.P., C.M., F.R.C.S.E., Gynecologist to the Grosvenor Hospital for Women. Pp. 219; 44 illustrations. London: J. and A. Churchill, 1923.

THIS monograph is a detailed study of the subject, written in a clear and interesting manner by one well informed on his subject. Statistics may or may not be misleading but a reading of the first chapter on Sterility and the State shows how important a problem is under discussion. The following four chapters are on the Physiology of Conception, Structural and Functional Causes and Medical and Operative Treatment. The single omission of note is the absence to any reference to trans-uterine insufflation of the Fallopian tube (Rubin's test). In all other respects, however, the book is fully abreast of the most recent literature on the subject.

W.

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A HISTORY OF MAGIC AND EXPERIMENTAL SCIENCE DURING THE FIRST THIRTEEN CENTURIES OF OUR ERA. By LYNN THORNDIKE, PH.D., Professor of History in Western Reserve University. In two volumes. Pp. 835 and 1036. New York: Macmillan Company, 1923.

THE medical man who is interested in the history of medicine will find these two volumes of great value not only as reference books but also to give him a broad knowledge of early attempts at scientific work up to the Fourteenth Century. He will find before him a book which deals in a most complete, and thorough manner with early experimental science and what is also most interesting, with early magic. The work is divided into two volumes and five books. The first volume contains three books: (I) The Roman Empire; (II) Early Christian Thought; (III) The Early Middle Ages; while Volume II contains books IV and V on The Twelfth Century and the Thirteenth Century. In going over the book in a non-critical way, the reviewer is struck with the clear exposition of the subject, the delightful methods of presentation used by the author and the undoubted authoritative-ness of the material. The influence of Roger Bacon and the importance of his contributions to science in the Thirteenth Century may be exemplified by the importance the author lays upon his work, devoting nearly eighty pages to the life and works of this wonderful man. Celsus is also thoroughly gone into and, to our English confrères who are obliged to read Celsus before they can go up for their final examinations, this admission to the text of a complete discussion of Celsus's work will seem eminently proper.

M.

**SYMPTOMS OF VISCERAL DISEASE.** A Study of the Vegetative Nervous System in its Relationship to Clinical Medicine. By FRANCIS MARION POTTENGER, A.M., M.D., LL.D., F.A.C.P., Medical Director, Pottenger Sanatorium for Diseases of the Lungs and Throat, Monrovia, California. Second edition. Pp. 357; 86 illustrations and 10 color plates. St. Louis: C. V. Mosby Company, 1922.

THE present interest in the physiologic aspect of clinical medicine and the uniqueness of Dr. Pottenger's contributions along the line of functional visceral neurology in the explanation of symptoms are undoubtedly the reasons for the ready appearance of a second edition of his book. As implied in this Journal's review of the original edition, it fills a distinct need in correlating much data in a field that is new to those who have not followed carefully the work of Mackenzie, Head and others. Considerable new material has been added. The illustrations are excellent. While it is true, as has been stated in criticisms of the work, that the terms used, such as viscerogenic, visceromotor, viscerosensory, and viscerotrophic are somewhat cumbersome, yet they are descriptive and for that reason helpful in clarifying a subject that is by no means simple.

The reviewer approves of the attempt to interpret certain symptoms in terms of vegetative nervous system disturbance and believes that Dr. Pottenger's studies in this field will be of great benefit to clinicians and teachers, but he cannot escape the feeling that some of the explanations offered are founded on, as yet, not sufficiently well established facts; for instance, the claim that magnesium sulphate solution when introduced into the duodenum dilates the bile duct sphincter and contracts the gall-bladder (which has not been proved) and that this results from vagus inhibition or sympathetic stimulation (again not proved).

M.

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**THE MEDICINE MAN.** By JOHN LEE MADDOX, PH.D., Captain (retired), U. S. Army. Pp. 330; 4 illustrations. New York: The Macmillan Company, 1923.

THE present volume is one of a series of books that the Macmillan Company are presenting to the medical profession on the more remote and the historical phases of medicine. The medicine man is partially a historical study but largely a sociological study of the character of Shamanism. It is a most complete exposition and one which has the added attraction of being well written and interestingly written, so that the medical man in his spare moments may read with pleasure what his distant connection, the medicine man, does for his savage patients.

M.

THE NEW PHYSIOLOGY IN SURGICAL AND GENERAL PRACTICE. By A. RENDLE SHORT, M.D., B.S., B.Sc. (Lond.), F.R.C.S. (Eng.), Member of Council, British Association of Surgeons; Examiner in Physiology for the F.R.C.S., Surgeon, Bristol Royal Infirmary. Fifth edition. Pp. 330. New York: William Wood & Co., 1922.

THE fifth edition of this small book has been considerably enlarged. It has been increased by the addition of three new chapters, one of which, Chapter IV on The Dietetic Factor in the Causation of Appendicitis, might well be omitted. Otherwise the book preserves its very interesting, non-controversial method of presentation throughout and should make most interesting reading for those interested in applied physiology. M.

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THE RIDDLE OF THE RHINE. By VICTOR LEFEBURE, Officer of the Order of the British Empire (Mil.); Chevalier de la Legion d'Honneur; Officer of the Crown of Italy; Fellow of the Chemical Society. Pp. 282; 5 illustrations. New York: E. P. Dutton & Co., 1923.

THIS volume is not truly in any sense a medical publication but it will appeal to the medical man who is interested in war and war chemistry. The book has to do almost entirely with the gases used in attack during war and the problems connected with their use. M.

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A SYNOPSIS OF MEDICINE. By HENRY LETHEBY TIDY, M.A., M.D., B.Ch. (Oxon.), F.R.C.P. (Lond.); Assistant Physician to St. Thomas's Hospital; Physician to the Royal Northern Hospital; formerly Assistant Clinical Pathologist and Medical Registrar to the London Hospital. Third edition, revised and enlarged. Pp. 985. New York: William Wood & Co., 1923.

THE popularity of this work is amply attested by the fact that within eighteen months the book has reached its third edition. There is presented in outline form an enormous amount of information, readily available for hasty reference or review, and should therefore recommend itself highly to practitioner, teacher and student. The present new edition has been thoroughly revised; many articles have been rewritten, including those on glandular fever, asthma, hayfever and others; while new articles have been added on a number of subjects. The new material added shows careful and conservative judgment on the part of the author. K.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

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**Cancer of Bladder and Radium Implantation.**—SMITH (*Jour. Urol.*, 1923, 9, 217) says that the implantation in bladder cancer of bare tubes of radium emanation of low potency or of radium bearing needles of 5 mgm. each, will cause complete necrosis of the tumor, provided, they are inserted 1 cm. apart, and are so placed that the entire periphery of the growth is brought within reach of rays of lethal power. Two classes of cases are suitable for this treatment: Small single papillary carcinomata, into the base of which bare emanation tubes may be deposited by intravesical methods; and sessile carcinomata or the bases of large fungating growths after destruction of the tumor by cautery, into which radium may be implanted through a suprapubic cystotomy. It is inadvisable to bring about the necrosis of a tumor more than 3 or 4 cm. in diameter, as the absorption of toxins from the infected slough is likely to prove fatal. The problem in treating cancer of the bladder by this method is to use enough radium to destroy the cancer, but not enough to destroy the patient. A number of cases of cancer of the bladder, in whom the growth could not have been excised successfully, have shown complete disappearance of the growth clinically, following the implantation of radium.

**Idiopathic Cyst of Common Bile Duct System.**—KIPF (*Arch. f. klin. Chir.*, 1923, 123, 635) says that idiopathic common duct cyst is a very rare phenomenon, for but 45 cases have been collected—usually discovered in the course of sections. The clinical picture in clearly marked cases gives characteristic but not differentiating symptoms of upper abdominal tumor, intercurrent jaundice, pain and stools without bile. Differential diagnosis must consider or exclude empyema or hydrops or gall-bladder, echinococcus and pancreatic cysts. The

pathological anatomy gives a cystic tumor in close relation to the body walls. The liver is thrust upward by the mass while the ligamentum hepato-duodenale is put greatly upon the stretch. The intrahepatic ducts are distended, the liver itself shows the typical picture of biliary cirrhosis. The histological picture confirms the gross findings: Chronic inflammation with marked round-cell infiltration. The cyst wall usually shares in these degenerative changes.

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**Study of Phenol-camphor Action in Joints.**—HEDRT (*Arch. f. klin. Chir.*, 1922, 122, 19) says the fundamental principles are small incisions, whenever possible; with drainage at the most dependent point; filling of the joint capsule with phenol-camphor; closure of the capsule and movement at the earliest time possible. Experimental researches show that the injection of phenol-camphor solution into the joint cavity does not injure the synovial membrane or the cartilage. The course of healing was quite uncomplicated, and greatly shortened. Cases followed up show very good function and radiographic studies in these cases showed no evidence of arthritis deformans.

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**Experimental Intraperitoneal Division of One Ureter.**—JONES (*South. Med. Jour.*, 1923, 16, 188) says that complete division of the ureter is an exceedingly grave occurrence, but not necessarily fatal. The chief symptoms in the author's animals were anorexia, weakness and diarrhea. Most of the animals were quiet the greater portion of the time. These symptoms are about the same as those found by other observers, except that they observed convulsions and coma rather frequently. The most striking features of our experiments as well as those of other investigators is the activity of the tissues in the vicinity of the severed ureter in preventing the spread of escaping urine. In some instances the reaction is so prompt that the ureteral opening is sealed at once. More frequently a urinary sac is formed by adhesions between the intestines, omentum and body wall. The amount of infection in the peritoneum, retroperitoneal tissue and abdominal wound was surprisingly small.

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**The Chronic Appendix.**—MAINGOT (*St. Bartholomew's Hosp. Jour.*, 1923, 30, 86) says that chronic lesions of the appendix are macroscopic; an appendix that looks normal is not in the least likely to give rise to symptoms and that, therefore, these must be looked for in other organs. The gridiron incision, while it may be useful in certain cases of acute appendicitis should never be employed when dealing with chronic appendicitis, for it is a physical impossibility to explore satisfactorily through McBurney's muscle-splitting incision.

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**Gangrene of Penis and Scrotum.**—ESAU (*Arch. f. klin. Chir.*, 1923, 123, 635) clarifies the etiology of this condition arising from so many possible sources. He groups his causes as follows: (1) The result of constitutional or generalized infections; (2) from urinary extravasation and infiltration; (3) from traumatic agencies, mechanical, chemical and thermal; (4) and most important, localized processes of infection. The whole picture parallels the so-called "phlegmons," which are often noted upon the arms and legs. Although the pathology is

superficial, the disease is very serious. The deeper processes of the gangrene vary—destruction by necrosis encompassing the entire genitalia only in fatal cases. Prognosis is especially guarded, for the subjects are often wasted by disease. The time at which treatment is instituted is important for every hour of delay is exceedingly costly. The author advises and outlines an energetic and radical surgical treatment.

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**Renal Aneurysms.**—VOGELER (*Deutsch. Ztschr. f. Chir.*, 1923, 176, 312) found that renal aneurysm arose directly from traumatism 18 times, while 11 cases were of spontaneous origin. The trauma was always of considerable violence; as falls from a horse, crushes between cars or against walls, or from knife wounds. The force was always acting directly over the kidney region. Two great factors in diagnosis besides the history are the tumor, and blood in the urine. Twenty-five of the cases were followed completely. The 18 unoperated cases showed after the trauma, bleeding, increasing intermittent hemorrhages, terminating in death. Of the 7 operated, only 1 died.

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**Blood Clotting Through Blood Transfusion.**—STEGEMANN (*Arch. f. klin. Chir.*, 1923, 123, 759) says that the direct action consists in the introduction of all the elements necessary for blood coagulation. However, but little is known of the hemolytic and coagulating principles. The vaso-constricting principle is of first importance. The indications for this method are, of course, quite limited. It is reserved for hemophilic states and those advanced stages of anemia following hemorrhage, in which heroic measures are necessary. The direct method of transfusion is preferable in these cases.

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## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**Studies On the Bio-assay of Pituitary Extracts.**—SMITH and McCLOSKEY (*Pub. Health Rep.*, 1923, 38, 493) discuss the unsatisfactory status of the artificial standards for the physiological assay of pituitary extracts. They describe a method for the preparation of a powder of uniform potency, representing the entire ecboic and pressor activity of the infundibular lobe of the pituitary gland, which does not deteriorate, and from which the active principles are readily extracted. Nine commercial extracts were purchased in

the open market and tested by the usual guinea-pig uterus method against the new infundibular extract. These commercial products varied greatly in activity, the strongest being no less than eight times as powerful as the weakest. One preparation which, according to the claims of the manufacturer, represented 30 gm. of fresh infundibular substance per 100 cc of solvent, assayed at less than 1 per cent. The author recommends that their powder of infundibulum be used as a standard and that manufacturers be required to make and to standardize their extracts to represent the activity of 4 mg. (equal to 30 mg. of fresh gland substance) per 1 cc of finished extract.

**The Postural Treatment of Diseases of the Bronchi.**—SCHAEFER (*Klin. Wchnschr.*, 1923, 2, 252) reports surprisingly good results from the Quincke treatment of diseases of the respiratory system whose chief symptom is profuse expectoration. The treatment consists of assuming that position which favors drainage of the diseased lung. When first instituted, the patient is taught to lie flat in bed without pillows and to remain quietly in this position for from thirty minutes to two hours. After two or three days, the foot of the bed is raised 30 cm. and subsequently the head is lowered below the level of the rest of the body and is supported by pillows on a low chair at the side of the bed. The patient lies on his healthy side to promote passive drainage of the diseased area. Splendid results are reported from the treatment in bronchiectasis, lung abscess, fetid bronchitis, and so on. In 1 case, the morning expectoration was decreased in the course of three weeks from the unusually large amount of 500 cc to nothing. If the upper lobe is the seat of the disease, the postural treatment is less successful, since drainage is difficult. No untoward symptoms (hemoptysis, nausea, dizziness, excessive coughing) complicated any of the cases treated by the postural method.

**The Mechanism of the Vomiting Induced by Antimony and Potassium Tartrate (Tartar Emetic).**—Emesis may occur as the result of direct or reflex excitation of the vomiting center. The reflex may arise from irritation or inflammation of any region of the alimentary tract or of some other organ. It has been shown that tartar emetic acts on the stomach to induce emesis after its oral administration, that only traces occur in the vomitus after its intravenous injection and that it does not cause emesis when applied directly to the vomiting center. WEISS and HATCHER (*Jour. Exper. Med.*, 1923, 37, 97), working with cats, found that the intravenous injection of tartar emetic caused typical vomiting movements after total extirpation of the entire alimentary canal. Vagotomy, while not always preventing nausea, invariably inhibited vomiting; simultaneous section of the vagi and extirpation of the stellate ganglia prevented both nausea and vomiting after intravenous injection of tartar emetic. Excision of the celiac ganglion and section of the vagi just below the diaphragm did not prevent vomiting. Cutting of the vagi prevents vomiting after the introduction of large but not of massive doses, and vagotomy has less effect on the emetic action of large doses introduced into the lumen of the duodenum than when these same amounts are introduced into the stomach. Atropine has very much the same effect on emesis as vagotomy, but

larger doses are required to suppress emesis when tartar emetic is introduced directly into the stomach than when it is injected intravenously. It seems probable, therefore, that the heart is the site of the origin of the reflex vomiting following intravenous injection of tartar emetic. The drug induces afferent emetic impulses which pass from the heart to the vomiting center by way of the vagus and to a less extent *via* the sympathetic nerves. The introduction of tartar emetic into the stomach arouses afferent emetic impulses which pass upward chiefly *via* the vagus, only a few being transmitted over the sympathetic nerves. The introduction of tartar emetic into the duodenum induces emetic impulses, which pass to the vomiting center over the vagus and sympathetic nerves. The path taken by the afferent emetic impulses induced by tartar emetic in the gastro-intestinal tract seems to depend on the innervation of the organ concerned and not on any selective action of the poison on the afferent nerve.

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**The Vitamin Content of Certain Proprietary Preparations.**—COWARD and CLARK (*Brit. Med. Jour.*, 1923, 1, 13) conclude from the experiments that under normal conditions of life an adequate supply of vitamins can be easily ensured by including in the diet a suitable amount of "protective foods,"—milk, butter, green vegetables and fruit—and that no advantage is gained by trying to obtain the substances in the form of such proprietary preparations as metagen, maltoline, roboline, virol, vitmar and Mellin's food.

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## PEDIATRICS

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UNDER THE CHARGE OF

THOMPSON S. WESTCOTT, M.D., AND ALVIN E. SIEGEL, M.D.,  
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**Suction in the Treatment of Laryngeal Diphtheria.**—LITCHFIELD and HARDMAN (*Jour. Am. Med. Assn.*, 1923, 80, 524) claim that the pseudomembrane is less intimately attached in the larynx and trachea than it is in the throat. Its removal does not leave as much bleeding. They report a case of laryngeal diphtheria in which their method relieved the obstruction immediately. They feel that suction is especially to be advocated for cases in which there is a low membrane, which cannot be reached by either intubation or tracheotomy. Laryngoscopic examination with suction in severe cases may be repeated when necessary every six or eight hours. It is interesting to note that many of the cases required but one treatment, and in these the membrane was loose in the larynx. In reference to the cases in which suction and intubation were performed, these being only 16 per cent of the total number of cases in which suction was employed, it was noted that intubation was necessary only because of a persisting edema. Convalescence from laryngeal diphtheria has been shortened



by sparing intubation patients, the strain that they were formerly subjected to in the desire to avoid intubation. The avoidance of intubation has no doubt diminished the incidence of chronic cases or patients who cannot endure the removal of the cannula. By employing visually guided suction the mortality was reduced. To perform suction the patient is wrapped in a mummy bandage as for intubation, and through a Jackson laryngoscope the membrane and mucous are aspirated by means of a No. 16 to 18, French silk or metal catheter, which is connected to an aspirating bottle, and in turn to an ordinary electric suction pump.

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**Bacteriology of the Urine in Acute Nephritis in Children.**—HILL, HUNT and BROWN (*Am. Jour. Dis. Child.*, 1923, 25, 198) studied 21 cases. They found the urine sterile in 16. In 2 cases, *Staphylococcus albus* was found. This was probably a contamination. A diphtheroid organism was found in 1 case and colon bacillus in 2 cases. The cases which showed the latter had high leukocyte counts with a good deal of pus in the urine, as well as blood and casts, due probably to a complicating pyelitis. Only 2 patients showed fever during the course of the disease, although it is possible and probable that in many cases fever was present at the onset before the child entered the hospital. One of these patients had cervical adenitis, which accounted for the fever, and 1 had a complicating pyelitis. The leukocyte count was elevated above 16,000 in 6 cases. In two of these, it was accounted for by the presence of a complicating pyelitis. In 3 cases, it was accounted for by the presence of a cervical adenitis. These results indicate that in most cases of acute nephritis in children, after the disease has once been established, there are no bacteria demonstrable in the urine and there are probable none in the kidneys. There is no fever and no elevation of the leukocyte count. These results do not rule out the possibility of bacterial infection at the very onset of the disease, and this is very strongly probable. According to some workers, bacteria are taken up by the polymorphonuclear and endothelial cells in the glomeruli, and in a very short time toxins are liberated by the rapid lysis of bacteria within the glomerulus. This causes the injury that is produced. This hypothesis is borne out by clinical observation on children suffering with acute nephritis. It is also possible that it is not the bacteria but soluble toxins absorbed from the infected focus, such as tonsils, cervical glands and the like produce the injury to the glomeruli.

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**Types of Organisms Found in a Series of Tuberculous Children.**—GORDON and BROWN (*Am. Jour. Dis. Child.*, 1923, 25, 234) in a total of 30 cases of tuberculosis in children under the age of twelve years, noted the bovine organism in 10, or 33.3 per cent. Of the total number of patients twenty-three were less than five years of age. In six of these the organism was the bovine. This represented a percentage of 25. The remaining 7 patients were between the ages of five and sixteen years, and of these there were 4 instances of bovine infection, or 52 per cent. From these figures, it can be seen there was a greater actual incidence of bovine infection in the children under five years of age, although the number of bovine cases in patients between the ages of five and

twelve was relatively greater. In the infants under one year of age, the bovine organism was identified only once. Of the total number of the cases, 22 were known to have been fatal. Of this number four, or less than 20 per cent, were of the bovine type. Autopsy was performed in 12 of the fatal cases. Of this group the cases, in which the point of origin of the infection was found in the alimentary tract, proved to be all bovine. The human bacillus was recovered from all of those cases in which the point of origin at necropsy was in the respiratory tract. In 5 cases out of the total number, the history indicated that the children were exclusively breast-fed. Four of these showed a human type of infection and 1 the bovine, and this probably had received cow's milk after having been weaned from the breast. Seven cases of the total number gave a definite history of either familial tuberculosis or contact with tuberculous persons. Of these, 6 cases proved to be infected with the human type of organism and one with the bovine type.

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**Internal Hemorrhagic Pachymeningitis in Infancy.**—BURHANS and GERSTENBERGER (*Jour. Am. Med. Assn.*, 1923, 80, 604) report 5 cases of internal hemorrhagic pachymeningitis, which were observed in their clinic within a period of three years. This corroborates the opinion of Finkelstein and Rosenberg, that the condition is more common in infancy than is generally believed. From the standpoint of etiology, in this series of cases, infections, especially diphtheria and syphilis, can be excluded in every instance but one, in which syphilis may be considered by some to have been a possible factor. From the standpoint of etiology, a poor state of nutrition can be positively excluded in 3 of these 5 cases, as 2 were exceptionally well-developed and nourished infants, and the third was also in a very good state of nutrition. The other 2 patients were in a very bad state of nutrition, but this was just as possibly a result as a cause of the pachymeningitis. Trauma can be implicated as a factor in 4 of the 5 cases. It would seem that subacute pachymeningitis from birth hemorrhage, rendered acute by further physical injury, would explain the development in some of these cases. In certain groups of infants there may be a definite predisposition toward the development of pachymeningitis. The prominent symptoms in these cases were retinal hemorrhage in 4 cases. In the one in which this was absent there was the largest collection of fluid in the subdural space. A positive fontanel puncture was obtained in 3 cases in which it was performed. In 1 case, a characteristic fluid was obtained by spinal puncture. In the fifth case puncture was not done because of parental objections. As the latter 2 children were about one year of age, and retinal hemorrhage was present, it is probable that a fontanel puncture would have given positive results. Convulsions were present in every case, but as convulsions occur as a result of other injuries and conditions their appearance is suggestive, but not pathognomonic. Bulging of the fontanels was absent throughout the period of observation in 3 cases, and in a fourth the fontanel did not bulge until the second admission, when it bulged slightly. In the fifth case there was slight bulging on admission. The absence of bulging of the fontanel does not speak against internal hemorrhagic pachymeningitis. A general state of collapse or widening

of the sutures may be sufficient to counteract the incroachment on the intracranial space by the development of a pachymeningitic cyst. Enlargement of the head was not definitely present in any of these cases. In only 1 case was there a possible enlargement. Nasal discharge was present in 3 cases and in 2 of these it was bloody in character. In 1 of these patients, the discharge did not develop the bloody character until long after marked evidence of the pachymeningitis had been observed. As no evidence of syphilis or diphtheria was found in any of this series, it may be concluded that the nasal discharge was a coincidence or a result of the pachymeningitis, and not a symptom of an infection responsible for the development of the disease. In two of the cases in which the calcium content of the fluid obtained through the fontanel puncture was determined, it was found to be decidedly lower than that of the blood serum, whereas the inorganic phosphorus content of the fluid and the blood serum was practically the same. Since these figures are the same as the results usually obtained by determinations on whole blood it would seem logical that the fluid in these subdural cysts is blood, unaltered except for the solution or digestion of all or a part of the red corpuscles. This is not supported by the amounts of sodium and potassium, which were the same as in the serum, nor by the percentage of protein, which showed a wide variation. The coagulation time and the bleeding time were normal in the 3 cases in which the tests were performed.

**Calcium Absorption in Children in a Diet Low in Fat.**—HOLT and FALES (*Am. Jour. Dis. Child.*, 1923, 25, 247) found that a marked reduction of fat in the diet of children changed the character of their stools from smooth, normal, alkaline, and well digested to acid, foul, with an excess of fermentation and undigested food residues. Whether this change was due to reduction of the fat or the increase of carbohydrate or to both factors is impossible to say. In 5 of the 7 cases, the calcium absorption was markedly reduced when the low-fat diet was taken, and in 3 cases, a negative balance was produced. In the other 2 cases, the stools were never entirely normal, even during the control period, and the absorption was not lower on the low-fat diet than it was on the control diet. These two children were very much alike so far as digestion and general symptoms were concerned. The chemical findings in these two cases were almost identical. It is impossible to offer any explanation of the difference of the results in these two cases and those obtained in the other five. The increase of calcium oxide excretion was in most instances due partly to the fact that on the low-fat diet the daily amount of total solids in the stools was markedly increased, and partly to the fact the calcium oxide percentage of total solids of the stool was higher. In all but 1 case, the total solids of the stool were increased on a low-fat diet. In 4 cases the calcium percentage of solids were increased. In all cases but one, the total ash percentage in the stool was higher on the low-fat diet. Although the results of these investigations were not altogether uniform, the indications are that a low-fat diet greatly diminishes calcium oxide absorption. Whether the calcium absorption is dependent on a definite relation between fat and calcium in the diet, or whether the fat intake influences the calcium oxide absorption chiefly by the maintenance of

proper digestive conditions, it is impossible to say. It is quite certain that a very low-fat intake brings about abnormal digestive conditions as judged by the type of stool. The conditions for proper calcium absorption are much better when the fat intake is generous.

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**A Comparative Chemical and Clinical Study of Boiled Butter and Cream in Infant-feeding.**—LOWENBURG (*New York Med. Jour.*, 1923, 117, 295) claims that volatile fatty acids exist in butter in even less stable combinations than in cream. By boiling butter slowly for five minutes, over 50 per cent of these acids are driven off. Boiling butter for two minutes is sufficient for clinical purposes, but from three to four minutes is a safer average. Sweet butter contains less volatile acids than does the salted. Boiling cream does not materially change its acid content. Boiled butter may be added advantageously in varying and gradually increasing quantities to skimmed milk formulas and to other food combinations. Boiled butter appears to be a more acceptable addition to milk formulas than does cream. The presence of flour or other forms of starch though acceptable to insure an even distribution of fat are not necessary essentials to the digestibility of boiled butter. Vomiting and diarrhea are neither inaugurated nor made worse by the addition of boiled butter, but may often cease. Constipation has been the rule, and the reaction of the stool has been found to have been feebly or markedly alkaline. All cases free of parenteral disturbances, to which this substance has been fed, have experienced a uniform gain in weight of from 1 to 2 ounces a day.

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## OBSTETRICS

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UNDER THE CHARGE OF

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**Delivery of the Arms and Head in Labor with Breech Presentation.**—Before a recent meeting of the Münchener Gynecological Society (*Monatsschr. f. Geburtsh. u. Gynäk.*, 1922, 59, 101) occurred an interesting discussion on this subject. Attention was called to the necessity of avoiding strong and forcible traction upon the body of the child in these cases. Smellie's advice to apply forceps to the after-coming head had been followed by the majority of obstetricians for a considerable time. Schroeder had opposed this, and this use of the forceps had been largely abandoned. In more than 40 cases in the Münchener Clinic since 1912, the forceps had been applied to the after-coming head with very good results. In discussion, the point was brought out that the successful use of forceps called for patience, skill and the avoidance of considerable force. The instrument must also be accurately applied to the sides of the child's head. In Continental clinics the Nägele forceps is often applied in the transverse

diameter of the pelvis. Attention was also called to the danger of cerebral hemorrhage in the infant, following laceration of the tentorium in breech extraction. In 291 cases reported in the literature, this accident occurred in 37 per cent of those children delivered by extraction. This is the result of pressure, much of which comes as the head passes through the partly dilated cervix. The best results are obtained by the use of forceps to the after-coming head and Kielland's comparatively new instrument is especially good for this purpose. It may be necessary to incise the cervix before extracting the head. Döderlein had obtained excellent results from the use of forceps to the after-coming head and was strongly in favor of its employment.

**Treatment of Placenta Previa by the use of the Dilating Bag.**—ZIMMERMANN (*Monatsschr. f. Geburtsh. u. Gynäk.*, 1922, 59, 94) presented a paper upon this subject, which was discussed at considerable length in the Münchener Gynecological Society's meeting. The criticism was made that while in the hands of an expert the use of the dilating bag in placenta previa gave excellent results, when employed by those not skilled and expert, the introduction of such a bag might separate the placenta and increase the bleeding. While this hemorrhage might not be severe and the blood pass between the placenta and the bag, it would still form an important element in turning the tide against the patient. Others preferred the extra-ovular use of the bag in these cases. This is thought to be the simpler method and productive of quite as good results as combined version and introduction of the bag through the placenta within the fetal sack. This method has a further advantage in that it can be applied by a physician without assistance in the home of a patient in cases where circumstances make it impossible to take the patient to a hospital or to summon further assistance. Others call attention to the danger of treating cases by the use of the tampon and combined version. One case was reported where in a multipara a firm tampon was applied and twenty-four hours later version was performed. This was followed by the death of the patient an hour afterward from hemorrhage caused by relaxation of the uterus. It was also thought exceedingly dangerous to proceed at once with the extraction of the child after combined version had been performed. Where patients enter hospital in good condition, not infected or greatly weakened by hemorrhage, it is possible to secure fairly good results. In the clinic in Bonn, Germany, in 72 cases the mortality among the mothers was 2.8 per cent, with a fetal mortality of 57.7 per cent. These results were obtained by the use of the dilating bag. Where combined version was employed, fetal mortality rose to 66.7 per cent. In another clinic, vaginal section had been employed successfully. In a series of 104 cases reported from one clinic, one-third of them were between seven and eight months in pregnancy. In 19 of these the treatment employed consisted of rupturing the membranes; in 15 Cesarean section was done successfully for mother and child, with the exception of one mother having contracted pelyvis, who died of grippe-pneumonia. There was a strong statement from one operator to the effect that he had never seen an efficient and properly applied vaginal tampon in these cases. He considered such application as useless and very apt to be followed by the development

of infection. Streit described the case of a multipara, aged forty-one years who had a contracted pelvis. This patient had previously had difficult labors. At the end of the sixth month she had a hemorrhage and remained in bed when the hemorrhage ceased. She was able after this to go about and entered hospital for the induction of labor. Hemorrhage occurred soon after. It was found that the child was in transverse position and that there was partial placenta previa. The membranes had not ruptured and a loop of the umbilical cord had prolapsed in the membranes. The bleeding from the lower uterine segment was excessive but was controlled by the tampon. Five hours later, after the introduction of the dilating bag, the case was terminated by version and extraction, with good results for mother and child. Attention was drawn to the comparative merits of dilating bags made of rubber and those made of animal membrane. It was also thought of the greatest possible importance that midwives be instructed to immediately send all patients to hospital who developed hemorrhages during pregnancy, and in such cases to abstain entirely from internal examinations.

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**Ectopic Gestation in the Ninth Month.**—TSCHAMER (*Monatsschr. f. Geburtsh. u. Gynäk.*, 1922, 59, 136) described the case of a woman, aged thirty-five years, who sixteen years previously had born a child in spontaneous labor. The patient had believed herself pregnant, but the abdomen grew less instead of greater in size. She had no pain or disability, and the movements of the child ceased, and the breasts no longer increased in size. A midwife made a diagnosis of the death of the fetus and prophesied its speedy expulsion. Five weeks passed without labor, and the patient went to the hospital, where she was given quinine, ergot and pituitrin, with the result of causing some dilatation of the cervix, but practically nothing else. Some time after, the abdomen decreased suddenly and considerably in size, and apparently fluid and solid material seemed to have been passed. The patient then became considerably weakened and depressed in general health and sought advice at the clinic. On examination, the patient was of moderate stature, anemic and weak, with fine rales and rough breathing over the lungs. Over the apex of the right lung there was dulness. The abdomen showed a central tumor arising from the pelvis and reaching above the umbilicus, whose exact nature could not be made out. No heart sounds or movements could be elicited. On vaginal examination, the cervix was hard and firm and apparently a difference could be made out between the uterus and the abdominal tumor. The rectal examination was negative. It was thought that the abdominal tumor might be a tuberculous mass or an ovarian cyst or pregnancy. On operation, the peritoneum was thickened and adhered to the wall of the tumor. On opening this there was a cavity filled with offensive reddish brown fluid and whitish masses. In this was the skeleton of a child at full term. The soft parts of the child had entirely disappeared, leaving the complete skeleton. The sack was emptied and cleansed, packed with iodoform gauze, and drained. A fistula with the bowel developed, which gradually closed, and the patient made a good recovery. On putting the pieces of the skeleton together, and measuring, it was found that the

child must have been about 45 cm. long, which corresponded with the patient's history. A similar case was reported in 1899 to the Obstetrical Society of Vienna by Knauer. In this case although the abdomen was opened, the fetal sack was taken for a malignant ovarian tumor, and nothing more was done, the abdomen being closed. Seventeen days later, the lower end of the abdominal incision opened and a portion of the fetal skeleton protruded, and ultimately the entire skeleton of the fetus at eight months was expelled.

**Labor Complicated by Rupture Into the Rectum of a Dermoid Ovarian Tumor.**—DAVIDSON (*Jour. Obst. and Gynec. Brit. Emp.*, 1922, 29, 376) describes the case of a multipara with delayed labor in whom the attempt was made to deliver by forceps. While traction was being exerted, a tumor, shaped like a sausage, bulged through the anus and on being pushed aside burst, extruding sebaceous material and hair typical of dermoid tumor. The child was delivered, the base of the tumor ligated and the mass was cut away. On examining through the rectum the ligature could be felt extending up to a tear in the bowel and leading into the peritoneal cavity. The abdomen was at once opened and the remainder of the tumor removed. Supra-vaginal hysterectomy was performed, and the perforation in the bowel was closed and drainage inserted through the posterior fornix. The patient's recovery was complicated by bronchitis, infection of the tonsils and pyelitis; later by bronchopneumonia. Two months after the delivery the patient was well with the pelvis clear. There was no discharge of fecal matter through the wound, and apparently the tear in the intestine closed completely. Colostomy might have been performed in place of suturing the bowel.

**Interstitial Pregnancy After the Removal of Tube and Ovary on the Same Side.**—MCINTYRE (*Jour. Obst. and Gynec. Brit. Emp.*, 1922, 29, No. 2) reports the case of a patient who for four and a half years had periodic attacks of sharp and cutting pain in the left iliac fossa and lumbar region. Abdominal section was performed, and the right tube and ovary were removed. Three years later she entered hospital with the history that eighteen months after her first operation she gave birth to a child in normal labor, the pregnancy having been normal and the child being nursed normally for some time. Menstruation returned six weeks after the birth of the child. There had been disturbance in menstruation, and the patient had felt ill for two weeks. Two days before admission, she fainted and later had severe pain in the abdomen. This disappeared on rest, followed by severe pain in the small of the back and vomiting. On admission to hospital the patient was collapsed; the abdomen soft but tender; the tenderness most marked in the left iliac fossa. There was dulness in both flanks, and a boggy fulness behind the uterus. On section there was a large quantity of blood in the abdomen, and on the right side of the uterine wall, where should have been the stump of the right Fallopian tube, there was a ragged cavity, containing blood clot. This was resected and the uterine wall sutured. The patient's recovery followed. On examining the specimen, chorionic villi were found, and no trace of the stump of the Fallopian tube. Microscopical examination showed

no trace of tissue belonging to the tube. The impregnated ovum had been in the uterine wall. At the first operation the stump of the tube was ligated and evidently the lumen of the tube must have been reëstablished. As the ovary on the right side was removed, the ovum must have been discharged from the left ovary.

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**Cullen's Sign in Ectopic Pregnancy.**—F. H. JACKSON (*Jour. Am. Med. Assn.*, 1922, 79, 1929) had made an interesting observation concerning Cullen's sign in ectopic pregnancy. He had occasion to examine a very obese young woman whose history indicated ectopic gestation. The abdomen was decidedly heavy, but the dark bluish discoloration at the umbilicus described by Cullen could not be made out. The patient was examined then in a dark room with a light directly on the umbilicus. The room was dark and one of the modern flash lights was focussed on the umbilicus. The greenish blue discoloration could then be made out. A vaginal examination in the case was suggestive but not definite. The patient was removed to hospital and operation disclosed an unruptured gravid tube, a large amount of free blood in the abdominal cavity and an ovarian cyst on the side corresponding to the gravid tube. The cyst was the size of an orange and was attached to the sigmoid and posterior broad ligament, with the gravid tube situated on top.

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**Unsuspected Pregnancy.**—MURRAY (*Lancet*, 1922, 2, 1073) reports the case of a woman aged twenty-four years, who twenty-nine hours before she was seen had been delivered of a 6½ pound child apparently at term. She had been married for three years, and during that time had passed through a severe attack of typhoid fever and had lost much weight. On her recovery she began to gain. Menstruation had always been scanty and infrequent, and following the typhoid there was for some time complete cessation. There was, however, a distinct history of some menstrual discharge each month during the nine months of pregnancy, and for this reason she supposed that this was the natural period. There had been no vomiting and the patient had felt no movements, had had no idea that she was pregnant, although the abdomen became large between the seventh and eighth months. After an attack of supposed indigestion there was pain in the abdomen. This increased in severity and the birth of the child occurred unaided followed by the normal delivery of the placenta. There were several lesions in the vagina which produced continuous oozing. These were closed under anesthesia and healed promptly. In the mother's efforts to extract the child the fingers had been introduced into the child's mouth and its palate was scratched in several places. So positive had the patient been concerning the occurrence of normal menstruation that she had made no preparations whatever for the birth of a child.

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**Lumbar Puncture in the Treatment of Eclampsia.**—SPILLMAN has revised the literature of this subject to determine whether in eclampsia this method of treatment is justifiable (*Am. Jour. Obst. and Gynec.*, 1922, 4, 568). The normal pressure in the spinal canal is 120 mm. of water. In eclampsia the pressure is found to range from 120 to 600. As to whether this treatment is dangerous in eclampsia it is



impossible to positively assert. Lumbar puncture is sometimes followed by cerebral complications which may be serious. Where infection of the blood-stream is present lumbar puncture predisposes to meningeal infection. As to the influence of lumbar puncture on the recovery of the patient, in 68 reported cases the mortality was 27.6 per cent. In 25 of the 68 cases convulsions ceased after the puncture, but in 2 of these cases the puncture obtained no fluid from the spinal canal. Among these 25 patients, 4 died; 3 of the deaths were due to streptococcus infection; 1 to pneumonia and 1 to hemorrhage into the brain.

It is usual to withdraw from 20 to 30 cc of fluid, but as much as 101 cc of fluid have been withdrawn at one time with recovery. The finding of blood in the spinal fluid does not mean that there has been fatal intracranial hemorrhage, although it is an indication of a serious condition.

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## GYNECOLOGY

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**Radiotherapy of Myopathic Bleeding.**—In reporting the final results of radiation in a series of 183 cases of myoma and myopathic bleeding, MILLER (*Surg., Gynec. and Obst.*, 1922, 34, 593) believes that he can prove that radiation will eventually supplant surgery in a large percentage of cases now treated by hysterectomy. Since it may be inferred that the writer is overenthusiastic in regard to the use of radium, he states that during the same period of time covering this series he has operated upon an equal number of cases, so that it can be shown that he appreciates the limitations of radium, and is by no means insistent that it can supplant surgery in all cases of myoma or essential hemorrhage. The age of the patient, the type and social situation, as well as the size of the tumor, the condition of the appendages, the evidence of previous infection and the general condition of the patient are all factors to be carefully weighed in determining the most satisfactory method of treatment. The most striking feature revealed in a review of both series of cases, those treated by radium and those treated by surgical intervention, is the increasing percentage of myomectomies performed where formerly hysterectomy would have been done. The prevalent idea that myomectomy is attended with a high mortality and that second operations are necessary in too large a percentage of cases to warrant conservatism is not borne out by the results obtained by competent surgeons. The decision to

resort to myomectomy in many cases which would have been subjects for hysterectomy formerly was prompted by the assurance that if myomectomy failed to control the hemorrhage or check the menstrual disorders radium would complete the cure without further surgical interference. With such assurance, the scope of conservative surgery has been materially widened, a larger number permanently relieved and the percentage of subsequent pregnancies has further justified the decision. The average time of exposure in young women in this series, that is, women under thirty-eight years of age, was twelve hours in cases of myomata. In women beyond this age, where it was not so important to preserve menstruation, the treatment lasted twenty-four hours. As a rule, 50 mg. of radium element was employed. This dosage produced permanent cessation of menstruation in women over forty years of age in 94 per cent of the cases. In the writer's earlier work, a second exposure was made within ten days or two weeks, but it was soon observed that this was unnecessary, and often caused discomfort that was persistent, and occasionally very distressing. In this series, 102 reported complete relief of the 107 cases of myoma, from hemorrhage within five months after radiation, while 2 other patients were relieved by a second application. In myopathic hemorrhage in women over forty years, a full radium dose (50 mg. for twenty-four hours) caused immediate cessation of menstruation in 20 per cent of the cases; 60 per cent menstruated once, 15 per cent menstruated irregularly, and the balance reported no relief and returned for a second treatment which was successful in all but 3 instances, 2 of which were relieved by a third exposure. Subsequent reports as to the menopausal symptoms are interesting. In women over forty years, in whom preservation of function was not considered important, about 60 per cent reported flushes and the usual phenomena of the climacterium. In about 20 per cent the symptoms were reported as severe, and almost invariably these cases had given a history of bleeding of the aggravated type. Profuse leukorrhea was noted in about 20 per cent of the cases, and a slight but persistent discharge was reported in 30 per cent, while in about 40 per cent it was absent, or was so slight as to cause no comment. Not infrequently, radium cured or markedly diminished a leukorrhea which was present before its application. The leukorrhea rarely lasted longer than six or eight weeks, although in several instances it was persistent after a year.

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**Vaginal Operation for Prolapsus.**—It is gratifying to CULLEN (*Am. Jour. Obst. and Gynec.*, 1922, 4, 544) to note that vaginal hysterectomy is gradually disappearing as a means of treating uterine prolapse and, in offering the method which has given him the most satisfactory results, he makes no claim of originality, but admits that he has combined measures from several different operations, especially those of Watkins and Coffe. The operation presented by the writer begins by drawing down the cervix and then making an incision all the way round the vagina fairly high from the cervix, after which a perpendicular incision is begun just below the urethral orifice and continued downward to the circular incision. The mucosa of the anterior vaginal wall is then dissected down from the transverse incision nearly to the external os and the triangular flaps above the transverse incision are dissected

away. The bladder, which prolapses into the wound, is then pushed up and separated from the upper part of the cervix and lower part of the body of the uterus. After the vesico-uterine peritoneal reflection is exposed, it is opened and instead of grasping the uterus with a tenaculum or other forceps, a figure-of-eight suture of chromic catgut is placed in the anterior wall of the uterus, going rather deeply in the wall but taking care not to enter the uterine cavity. This suture is now tied and used as a tractor. This exposes more of the fundus and a second figure-of-eight suture is placed and tied. After three such sutures are in place, the end of each is rethreaded, passed through the peritoneum where it was opened, and then through the edge of the vaginal mucosa. After these sutures have been placed they are clamped, and a small gauze pack is temporarily placed between the bladder and fundus in order that no blood may escape from the vagina into the peritoneal cavity. Strong traction is now made on the uterus from below and the cervix is cut half way through transversely. The cervical canal is then well dilated and the cervix is then completely severed, removing the adjacent posterior vaginal wall with it, as outlined by the primary transverse incision. Douglas's cul-de-sac is occasionally accidentally opened while the mucosa of the posterior vaginal wall is being dissected free, but when this happens it is of little consequence if the rent is immediately sutured with catgut. The vaginal edges remaining are now united to the cervix by interrupted sutures and then the original fixation sutures in the uterus are tied, bringing together the anterior wall of the vagina. The perineum is then repaired and a most satisfactory result will follow according to the writer.

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**Myomectomy.**—In recent discussions on the treatment of uterine fibroids, the alternatives of hysterectomy on the one hand and roentgen-ray and radium treatment on the other have generally been dealt with as though they exhausted the possibilities of treatment. Myomectomy has been almost entirely overlooked. GILES (*Lancet*, 1923, 204, 178), who is surgeon to the Chelsea Hospital for Women in London, holds the view that in the majority of cases of fibroids requiring surgical treatment, hysterectomy is the more suitable and also the more satisfactory operation, and the scope of myomectomy is restricted to the minority of cases. Hysterectomy requires no justification; it is generally accepted as a sound procedure, surgically and clinically. But myomectomy needs to be justified by its results, and reasons must be stated as to why it should be preferred; its limitations must also be acknowledged and the conditions of its suitability defined. The outstanding claims for myomectomy are: (1) That the uterus is preserved for the important function of child-bearing; and (2) that the patient is thereby spared the mental distress of feeling that an essential part of her womanhood has gone. The broad-minded advocate of myomectomy will at once concede that in a woman who is past the child-bearing age, the first claim disappears and the second has only an academic existence, although there may be reasons for preserving the uterus that are not founded on its child-bearing function. But we may properly narrow the issue to the consideration of myomectomy *versus* hysterectomy in the child-bearing period. We may glance

first at the immediate results; namely, the mortality as compared with hysterectomy; for this purpose the writer believes that his own statistics will serve as well as any. The figures (to the end of December, 1922) are as follows: Hysterectomy for fibroids, 1004 cases, 17 deaths, mortality 1.69 per cent; myomectomy, 173 cases, 3 deaths, mortality 1.7 per cent. There is thus very little difference in the mortality of the two operations, certainly not enough to make this a deciding factor in the choice of operation. What is the likelihood of a recurrence of fibroids? In the present series of 49 cases examined or reported upon by their doctors, the uterus was normal in size without fibroids in 41 cases; it was enlarged without fibroids in 3 cases; in all 44 cases without fibroids, or 90 per cent. In regard to the effect on the menstrual losses, in the present series he excludes 6 cases where the menopause preceded or synchronized with the operation. Of the remaining 47 cases, menstruation was normal and moderate in 36, or 75.1 per cent; and in 11 cases it was profuse, either at first or later on, or there was intermenstrual loss. Taking all the cases together, we find that of 83 cases menstruation was normal in 67, or 80.7 per cent. The conclusion is that there is liability to menorrhagia or metrorrhagia after myomectomy in about 20 per cent of cases. This result is not altogether surprising because it is clear that unless we open the uterine cavity every time we do a myomectomy, some small intra-uterine growth may easily be overlooked. In regard to the serviceability of the uterus for child-bearing after myomectomy, this report shows that of 50 women who had the chance of conceiving after operation, 14 became pregnant, or 28 per cent. The author, therefore, claims that judged by the criterion of results, the advantages of myomectomy definitely outweigh the disadvantages in the surgical treatment of uterine fibroids in a restricted class of cases. His own feeling is sufficiently expressed in the fact that of 1177 cases of uterine fibroids treated surgically, hysterectomy was done in 1004, or 85.3 per cent. This proportion of myomectomy to hysterectomy was thus 1 to 6, showing that he applies myomectomy only in a restricted class of cases. Fibroids associated with pregnancy do not necessarily call for surgical treatment. When they are causing no symptoms, and do not seem likely to interfere with labor, it is best to leave them alone, always provided that the patient can be kept under observation so that operation can be undertaken if urgent symptoms arise, and that the medical attendant is on the lookout during labor. Myomectomy during pregnancy is indicated in three groups of conditions: (1) When the tumor or tumors appear to be increasing rapidly in size; (2) when the patient is suffering from pain, pressure symptoms, or indications of septic or degenerative changes in the tumor; (3) when the position of the fibroids makes it probable that labor will be obstructed, in which case myomectomy is done for the purpose of avoiding the necessity for Cesarean section and of allowing the confinement to take place naturally.

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**Treatment of Chronic Leukorrhea.**—A dozen years ago, dilatation and curettage was probably the most frequently performed gynecological operation. This held true for the most prominent clinics as well as for less well known operating rooms. Not only was this a usual operation, but the reason assigned for scraping the uterus was most often

a chronic infection, variously designated as chronic metritis, endometritis or leukorrhea. Observance of the futility of this procedure, particularly its limited value in attempts to relieve discharges, stimulated in CURRIS (*Jour. Am. Med. Assn.*, 1923, 80, 161) a desire to learn something about chronic leukorrhea and chronic infections of the uterus. These efforts in turn eventually led to a study of diseased Fallopian tubes. He found that a small percentage of chronic leukorrhea cases are due to diffuse pelvic infection, to congested displaced organs and to other kindred lesions, but the overwhelming majority belong to the infected cervix—Skene's duct group. During the last four years he has treated the most severe and persistent cases of chronic leukorrhea as follows: The vicinity of the urethra is searched for infected Skene's ducts and urethral glands. Diseased foci are threaded on the blunt end of a needle, the tract is laid open with a knife, and the lining is fulgurated or otherwise cauterized. The cervix is thoroughly dilated, and radium is introduced into the cervical canal for the purpose of producing atrophy of the infected hyperplastic glands. Recovery has resulted in 90 out of 104 cases treated according to this plan. Whether the endocervix is treated with radium or thoroughly excised according to the method of Sturmdorf is perhaps immaterial. We must remember, however, that the glands in the region of the urethra also demand examination and appropriate attention. The work of the writer in the field of uterine infections has been one of the outstanding contributions of the past decade and his conclusions and recommendations should be carefully considered by all interested in this line of work.

**Pyelography.**—A rather extensive experimental as well as practical study of the various chemicals used in pyelography has been made by LOWSLEY and MULLER (*Jour. Urol.*, 1923, 9, 1), as a result of which they have come to rather definite conclusions as to the proper technic as well as proper solution which should be used in this helpful diagnostic procedure. The technic which they recommend is to cystoscope the patient as usual, catheterizing the ureters with lead catheters. Specimens are collected from each ureter and sent to the laboratory for bacteriological, chemical and microscopical examination. A phenolsulphonephthalein test is then performed to determine the efficiency of each kidney before the pyelogram is made. Two roentgenograms are taken before the injection of the opaque material, one of the kidneys and upper ureters and another of the bladder and lower ureters. Sodium iodide, 20 per cent is then carefully injected with a special syringe and as soon as the patient complains of a feeling of fullness some of the solution is allowed to run out and then another roentgenogram is made of the upper tract and one of the lower tract as was done before the injection. A fifth roentgenogram is made with the patient in the erect posture, the catheters having been withdrawn to the ureteral orifices and sodium iodide injected during this withdrawal. They have found that many strictures and other ureteral defects are brought out in this way which are not discernible in the prone position and with the ureteral catheters in place. The sodium iodide is usually drained off by reinserting the catheters, thus relieving instantly the pressure exerted by the injection. It was formerly their

practice to do a pyelogram on only one kidney at a time, but since they have been using sodium iodide they unhesitatingly do bilateral pyelograms. They have found that 20 per cent sodium iodide solution is more satisfactory as a pyelographic medium than any other solutions as it casts a deeper shadow, is non-toxic, non-irritating and is easily prepared. They believe however, that pyelography should be done only in selected cases. Persons suffering from acute or subacute infections of the kidneys, those who are emaciated or in a weakened condition should not be subjected to this examination.

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## PATHOLOGY AND BACTERIOLOGY

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**The Intestinal Flora in Mouse Typhoid Infection.**—Inasmuch as some mice, in the course of epizootics or after artificial feeding of a strain of *B. pestis caviæ*, do not develop mouse typhoid, it is evident that the mere presence of the organism is not the sole factor, in every case, in producing the infection. In order to determine the other necessary factors, WEBSTER (*Jour. Exper. Med.*, 1923, 37, 21) determined the normal intestinal flora of 58 mice, receiving a regular diet of bread and milk, by culturing the stools of 50, and the contents from duodenum, ileum, cecum, colon and sigmoid of 8. In addition, 33 mice were divided into groups of 16 and 17, respectively. One group was fed bread and milk for five days, the other raw beef muscle and water for the same period of time. After determining the flora, the animals were given, by stomach tube, 0.5 cc of an eighteen-hour broth culture of *B. pestis caviæ* diluted 1 : 100. It was found that in those mice fed on bread and milk, *B. acidophilus* and *B. bifidus* dominated the floræ about 25 to 1, whereas, when the diet was changed to meat and water, the floræ changed rapidly, the Gram-negative bacilli and certain putrefactive organisms outnumbering all others. This flora did not change after the instillation of *B. pestis caviæ* into the stomach and was the same in those mice which resisted the infection as in those which had succumbed. Furthermore, the mice receiving meat and water and showing a colon, *B. diffluens* and *B. welchii* flora were equally susceptible to mouse typhoid, as were the mice fed on bread and milk and showing the acidophilus flora.

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**Microbic Virulence and Host Susceptibility in Mouse Typhoid Infection.**—From previous observations on an experimental epizootic

of mouse typhoid by a member of the paratyphoid-enteritidis group, *B. pestis cavia*, it was learned that regardless of the number of bacteria ingested, some mice proved refractory to infection by the gastrointestinal route, the normal portal of entry. Continuing his work along these lines, WEBSTER (*Jour. Exper. Med.*, 1923, 37, 231) conducted seven experiments, utilizing over 300 white mice from the stock breeding rooms of the Rockefeller Institute, 26 from Pennsylvania and 28 from New Jersey. All mice were of uniform age and weight, received a diet of bread and milk and were placed in separate sterilized jars. Control stool cultures and blood-agglutination tests were made. All animals were injected *per os* by stomach tube with fixed doses of *B. pestis cavia*. At short intervals thereafter the stools and blood were examined for the ingested bacteria, the general character of the fecal flora was ascertained and the blood tested for homologous agglutinins. It was found that the mice, under these conditions of experimentation, varied in their susceptibility to mouse typhoid infection. In any series 20 to 30 per cent showed no sign of infection; 5 to 10 per cent presented symptoms of the disease, yielding positive blood cultures and recovered with or without homologous agglutinins; 70 to 80 per cent developed positive blood cultures, and succumbed in a more or less constant ratio relative to time. While the New Jersey mice followed a curve quite similar to that of the 520 standard controls, the Pennsylvania mice were more resistant to infection. The strain of *B. pestis cavia* employed over a ten-month period of experimentation showed no permanent change in virulence.

**Contribution to the Manner of Spread of Mouse Typhoid Infection.**—Having called attention to the fact that the spread of mouse typhoid in a given mouse population is determined by three factors, namely, the special and quantitative distribution of the bacilli, the virulence of the microorganism and the susceptibility of the host, and having described experiments dealing with the last two variables, WEBSTER (*Jour. Exper. Med.*, 1923, 37, 269) conducted contact experiments in such a manner that healthy mice and mice inoculated by means of a tube *per os* were brought together in a way calculated to vary the concentration of the available infecting bacilli by altering the ratio of infected to non-infected animals. Two experiments, employing 100 mice each, were performed. In the first, when the proportion of inoculated to the uninoculated mice was 5:1, the mortality curve of contact mice agreed closely with that of the control curve based on the 20 mice each of which was given a fixed dose of the bacilli, whereas when the ratio was 1:1, the mortality of the contact mice was virtually negligible. In the second experiment, it was demonstrated that crowding increased the mortality. From the results of the several investigations and after comparing the resultant curves with the standard curve, the author concludes that his results "indicate that, with a given susceptible mouse population and a certain strain of mouse typhoid bacilli, the sporadic and epidemic prevalences of mouse typhoid are determined by the special and quantitative distribution of the bacilli. Under circumstances in which the entire mouse population is so exposed as to be in direct contact with an infecting dose of the mouse typhoid bacillus, the nature of the resulting mortality curve

depends upon the quality of susceptibility of the individuals composing the population."

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**Comparative Study of the Kahn and the Wassermann Reactions for Syphilis.**—IDE and SMITH (*Arch. Dermat. and Syph.*, 1922, 6, 770) presented a preliminary report on parallel tests in an unselected series of 2165 serums, using the precipitation reaction, as described by Kahn, and the Wassermann reaction, employing sheep cells and guinea-pig complement. Two antigens were used in each case, an absolute alcohol extract of human heart muscle, reinforced with 0.4 per cent cholesterin and an acetone and lipoid extract, with cholesterin as proposed by Kolmer. The fixation period varied from fifteen to eighteen hours in the ice-box. Of the 2165 serums, the results of the two tests were identical when more than two plus positives were counted. The authors believe that the Kahn precipitation reaction is almost as valuable as the Wassermann reaction on blood serum but indicate that it is not as efficient on spinal fluids. They state that anticomplementary serums give no difficulty with the Kahn test, such serums being either positive or negative.

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## HYGIENE AND PUBLIC HEALTH

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UNDER THE CHARGE OF

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**Results of Active Immunization with Diphtheria Toxin-antitoxin in the Public Schools of New York City (Manhattan and Bronx).**—ZINGER (*Reprint Series, Dept. of Health, New York City*, No. 100, July, 1922) states that the immunity response to the same mixture of toxin-antitoxin varies greatly in different groups of children. A preliminary stimulation of the tissue cells in Schick-positive children caused by repeated exposure to infection with the diphtheria bacillus seems to enable the cells to give a better response to injections of toxin-antitoxin than in other children whose cells have not been previously stimulated by such exposure. This is the case even though these exposures have been slight and have not been apparent in the form of a perceptible increase of antitoxin in the circulating blood. After a first series of toxin-antitoxin injections, the immunity response to the second series did not follow the same inverse ratio noted between the original susceptibility of the children in a school and the percentage of successfully immunized children in the same school. Three doses of toxin-antitoxin, each from 1 to 1.5 cc, injected at intervals of one



week, give much better immunity results than 2 doses of the same amount injected one week apart. A longer interval between the injections of toxin-antitoxin has the advantage in allowing the local reaction to disappear more completely before the next injection of toxin-antitoxin is given. There may also be a better antitoxin response when the injections are given two weeks apart. At least six months should be allowed to elapse after the injections of toxin-antitoxin before the Schick retest is made to determine accurately the development of an active immunity. A second series of two or three injections of toxin-antitoxin should be given to those who have not become immune after the first series. There are a few children who fail to develop immunity after toxin-antitoxin injections even when they are given several series of injections. In the schools reported, from 70 to 93 per cent of children were rendered immune after two series of toxin-antitoxin injections. There is practically no danger from anaphylaxis, either in repeating the injections of toxin-antitoxin or in giving toxin-antitoxin after a preliminary injection of antitoxin.

**Toxin-antitoxin Immunization Against Diphtheria.**—PARK (*Jour. Am. Med. Assn.*, 1922, 79, 1584) summarized the results of twenty-five years of experimental and practical investigation of the immunizing effect of toxin-antitoxin injections and the value of the Schick test as follows: Three injections, 1 cc each, of a suitable toxin-antitoxin mixture spaced one or two weeks apart, will cause about 85 per cent of susceptible children or older persons to develop sufficient antitoxin to give the negative Schick reaction and produce marked, if not absolute, protection against diphtheria. The development of the immunity is slow. An amount of antitoxin sufficient to prevent the positive Schick reaction develops in different children in from one to six months after the receiving of the injections. Antitoxin, as heretofore, must continue to be used to produce immediate immunity. The duration of the immunity in at least 90 per cent of the children is for more than six years and probably for the remainder of life. There seems to be no difference in this respect between these, and those who develop antitoxin naturally. Toxin-antitoxin injections should not be given within two weeks after an injection of antitoxin; otherwise the toxin is slightly overneutralized and the resulting development of antitoxin is lessened. Mixtures made from old toxin and antitoxin are fairly stable and may be used for a period of one year. Even such preparations are at their best when first sent out, as the mixtures slowly tend to become at first neutralized and then slightly antitoxic. This change gradually lessens the immunizing power of the toxin. The toxin-antitoxin should be kept cool and in a dark place; it is best to use the mixtures within three months after their final preparation. A toxin-antitoxin mixture of stabilized materials which is safe when it leaves the laboratory cannot become more toxic on being kept. No serious effects ever have resulted from the injections given to the tens of thousands of the New York children in the past seven years. The Schick test is an extremely reliable means of separating those individuals who have antitoxic immunity from those that have none. Although a simple test, it must be carried out with extreme care. The toxin must be retained intracutaneously, and the toxin

must be neither 25 per cent more nor less than the desired amount. It is extremely important to choose glass of suitable chemical composition for the containers in which the toxin is to be placed, as otherwise rapid deterioration may take place. The preliminary Schick test is usually omitted in children under three years of age. This is for two reasons: (1) Two-thirds of these children require the toxin-antitoxin injections anyway; (2) it is not certain whether those that do give the negative reaction are immune because of an unusual persistence of the antitoxin given them by their mothers, or because of the active development of antitoxin in their own bodies. After this age the test is desirable, but it is often omitted. Thus, in practical school work, the first Schick test is frequently omitted in children up to six years of age because it is easier to inject the children at once rather than to delay for the test. At this age the percentage of children requiring immunization is still high, and the annoyance from the injections is slight. The omission of the preliminary Schick test facilitates the introduction of the immunizing injections in the schools. Above the age of six years, the preliminary Schick test should be made whenever practicable. No child should be pronounced immune from diphtheria because of having received three immunizing injections of toxin-antitoxin. A negative Schick test is absolutely necessary before one can properly make such a statement or issue a certificate. The use of the control-protein test made with the heated toxin is advisable at all ages when a careful separation of the pseudonegative reaction from the combined positive reaction is important. As with the Schick test, it is frequently omitted because of local conditions. The older the child the more likely it is to be immune and to give a confusing protein reaction. In children under five years of age, the protein reaction seldom confuses the picture if the Schick tests are read as late as on the fourth day; between five and seven years of age, the control does not help greatly in more than 5 per cent. In older children and adults, not only does the control protein test help us to decide more correctly in about 10 per cent of doubtful reactions; but when it is marked it also indicates with some probability those persons who are likely to have the marked local and constitutional reactions from the toxin-antitoxin injections. The toxin-antitoxin injections are inadvisable before the age of six months. During this time most of the infants retain the antitoxin received from their mothers. Up to the age of three months, immunizing injections are usually ineffective as the infant tissues do not respond sufficiently during this period to the toxin-antitoxin to produce antitoxin. Under usual conditions, it is probably safe to wait until the infant is nine months old and then to give the injections at the first suitable occasion. During the first three years there is almost no annoyance from the injections. As the child grows older, the danger from diphtheria gradually lessens, and the percentage of those developing annoying local and constitutional reactions slowly increases. The immunization of school children in acting to prevent their contracting diphtheria also lessens the exposure to infection of the younger children of preschool-age in their families. There appears to be no difference in the degree of immunity between those individuals who have developed antitoxin from natural causes and those who did so because of the stimulus of the toxin-antitoxin

injections. Institutions in which the children have been given the immunizing injections have been remarkably free from diphtheria. The school children who have been injected have had one-fourth as many cases as the untreated children, and these cases have been of less severity.

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**The Tetanus Bacillus as an Intestinal Saprophyte in Man.**—TENBROECK and BAUER (*Jour. Exper. Med.*, 1922, 36, 3, 261) state that the only reliable method that can be used for the detection of tetanus bacilli is the culturing of the suspected material, the isolation of tetanus-like organisms and the demonstration that the pure cultures form a spasm-producing toxin that is neutralized by tetanus antitoxin. Using this method, the authors demonstrated tetanus bacilli in 34.7 per cent of stools from 78 individuals in Peking. The tetanus bacillus grows in the digestive tract, for it is present in individuals who have been on a practically sterile diet for a month or more, and one individual may eliminate several million spores of tetanus bacilli in a single stool.

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**The Relation of Physical Defects to Sickness.**—COLLINS (*Public Health Rep.*, 1922, 37, 2183) studied records of physical examination and school attendance during the school session 1920-21 kept for 3786 children in four fairly representative localities in Missouri. These children were classified according to physical condition and the absences from sickness and from causes other than sickness were compared by age groups for children of different physical conditions. The author states that children with no defects were absent from school on account of sickness consistently less than those with defects. Children with enlarged or diseased tonsils were absent more than children with no defects, and those with enlarged or diseased adenoids or tonsils associated with other defects were absent considerably more than those with enlarged or diseased tonsils only. Decayed teeth showed little or no effect on absence, and defective vision failed to show a consistent effect on absence from school on account of sickness. Absence from causes other than sickness showed variations somewhat similar to absence from sickness; the groups with defects were absent more than the group with no defects.

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ORIGINAL ARTICLES.

THE USE OF FAT IN DIABETES MELLITUS AND THE  
CARBOHYDRATE-FAT RATIO.\*

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AND

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**Introduction.** In diabetes mellitus, the chief disturbance of function is the inability of the body to utilize carbohydrate. Every gram of protein metabolized yields over half its weight in carbohydrate. Therefore, the chief source of energy must be either endogenous or exogenous fat. The complete combustion of fat, however, is limited by the amount of carbohydrate that the body can use, for it is known that glucose must be burned in order to oxidize fat to carbon dioxide and water. Incomplete oxidation of fat results in the production of ketone bodies, and when these substances occur in large amounts, clinical acidosis may result. Until recently, it has been the custom to use relatively small amounts of fat in the diets of diabetics. The relatively high caloric value, the protein sparing action and the relatively low specific dynamic action of fat are advantages in favor of its use, which frequently make it desirable to feed it in the largest amounts possible without producing any significant ketosis. This may be done without danger if we know the amount of fat that is com-

\* The work reported in this paper was presented in abstract before the Society for Experimental Biology and Medicine, Proceedings, 1920, 18, 109, and Association of American Physicians, Transactions, 1921, 36, 266.

pletely oxidized through the oxidation of a given amount of carbohydrate. In view of the importance of this question, we have undertaken the problem of determining whether anything like a fixed ratio for this relationship exists; whether such a ratio is alike in normal and diabetic persons, and whether it is the same for all cases of diabetes, and if so, of determining its limits so that it may be applied in dietary treatment.

**Literature.** This subject has received much attention for many years, and its importance is quite generally appreciated. The chemical mechanism involved in the probable reactionary substances, acetone bodies or precursors, and glucose has been discussed by Geelmuyden,<sup>1</sup> Woodyatt,<sup>2</sup> Ringer<sup>3</sup> and Shaffer.<sup>4</sup> Only recently has any work of a quantitative nature appeared leading to practical appreciation in the dietary treatment of diabetes. Zeller,<sup>5</sup> in his studies upon the influence of fat and carbohydrate upon protein starvation, observed that when the nitrogen intake was reduced to a very low level, and the fat and carbohydrate ingestion so adjusted that the carbohydrate fraction of a diet, adequate in caloric value, amounted to 10 per cent of the total calories—approximately 1 gm. of carbohydrate to 4 gm. of fat—there was a marked increase in the amount of ketone bodies in the urine. When the carbohydrate intake was reduced still lower, to 5 per cent, there was a large amount of ketone bodies present in the urine, associated with headache and general malaise. Lusk<sup>6</sup> made the suggestive comment on Zeller's experiment that "In the normal combustion of fat, each molecule of  $\beta$ -oxybutyric acid, which is the end-product of the oxidation of each fatty acid, requires the presence of a triose molecule." The work of Lang<sup>7</sup> may be cited as suggestive of a definite carbohydrate-fat ratio for the complete oxidation of the fatty acid radical of the latter, although the experiments are not devised to establish a very close quantitative relationship. The subject has received a new impetus through the interesting work and discussion of Shaffer.<sup>4</sup> Furthermore, Newburgh and Marsh<sup>8</sup> have reported success in the treatment of diabetes with diet high in fat. Evidence is brought forward by Shaffer<sup>4</sup> that *in vitro* acetoacetic acid rapidly disappears in the presence of glucose and hydrogen peroxide in an alkaline solution. Turning his attention to the process involved in the organism, he presents interesting calculations of the ketogenic and antiketogenic factors metabolized, first suggesting that 1 molecule of glucose (antiketogenic) must be formed to oxidize completely 1 molecule of fatty acid (ketogenic), and later 1 of glucose to 2 of fatty acid. Following Shaffer, Woodyatt,<sup>9</sup> Hubbard and Wright,<sup>10</sup> Wilder, Boothby and Beeler,<sup>11</sup> and others have presented evidence together with a discussion of certain theoretical considerations bearing on a definite carbohydrate-fat ratio. Our studies were begun in the autumn of 1919, as a result of its importance in the dietary treatment of diabetes, and the sugges-

tive work of Zeller, with Lusk's comments, and without the knowledge of the work then in progress in Shaffer's laboratory.

**Experimental.** The endeavor was made to eliminate in the experimental procedure as many variables as possible in order to simplify the interpretation of results. In our subjects, the following conditions were successfully established in most instances.

1. The patients selected presented uncomplicated diabetes mellitus.

2. For several days previous to, and at the beginning of the experiment, the urine gave no reaction for acetone and acetoacetic acid by sodium-nitroprusside test, and the daily excretion of the ketone bodies estimated quantitatively was within normal limits.

3. The diet was so adjusted that the urine did not reduce Benedict's solution.

4. Nitrogen equilibrium was maintained throughout the experiment, thus tending to stabilize, so far as possible, the protein factor in the intermediary metabolism.

5. There was little change in body-weight.

The procedure has been, by dietary measures, to render the urine free from sugar and ketone bodies, and to determine the food tolerance. When this is established, the subject is given a diet, the total calories of which (together with the protein quota) are calculated to establish and maintain nitrogen equilibrium. The carbohydrate and fat are varied isodynamically with at first relatively high carbohydrate, gradually increasing the fat until ketone bodies appeared in the urine, as evidenced by qualitative tests, or showed by quantitative estimation a definite increase over the earlier average excretion. The protein quota of the diet, approximating 10 per cent of the total calories, was kept constant throughout the experiment.

When nitrogen equilibrium and weight are maintained for periods of days or weeks, it seems probable that the daily total metabolism is fairly constant, and furnished by the food taken. We assume that the carbohydrate taken in the food is utilized since the patient remained sugar free. Protein metabolism was estimated from the urine nitrogen. Examination of the stools for macroscopical and microscopical fat, as well as quantitative estimations of the daily amount (3 to 7 per cent) in 2 cases, have convinced us that at least 95 per cent of the ingested fat is absorbed and may be utilized. In this connection, attention may be called to the work of Hill and Bloor,<sup>12</sup> indicating that normally all fat fed is absorbed, and that the fat in the feces represents fat excreted. However, fat excreted is not utilized.

In those cases where nitrogen equilibrium could not be maintained, and where weight loss was present, the fat burned was calculated from the difference between the calories furnished by the protein and carbohydrate, metabolized, and the estimated total

metabolism. Estimates were obtained from basal metabolism studies or the formula of Du Bois.<sup>13</sup> Twenty per cent was added for rest in bed, and 40 per cent for being up and about the ward.

The following chemical methods were employed: For urine nitrogen, the Kjeldahl method for total nitrogen; for acetone bodies, the method of Van Slyke and Fitz;<sup>14</sup> for blood sugar, the method of Folin.<sup>15</sup> All the determinations were made in duplicate and checked.

Basal metabolism determinations were made with Tissot gasometer.

In the main, all diets are calculated from Atwater and Bryant's tables.<sup>16</sup> For certain food values, *Bulletin* 220, Pt. II, Connecticut Agricultural Experimental Station, and data furnished by the Department of Nutrition of Columbia University and the Presbyterian Hospital were consulted. The fat percentage of the cream used was determined directly by analysis. All food was cooked in the dishes in which it was served; all weighings were checked and corrections made for food returned. The value of the caloric estimations of these diets is discussed later in this paper.

TABLE I.

Case No.	Increase in ketone bodies shown by test.	In nitrogen equilibrium, No. wt. loss.	Fat burned estimated.	Ratio for period of increase.	Length of shift periods.
I. . . . .	Qual.	Yes	No	2.5	Daily shift.
II. . . . .	Quan.	No	Yes	3.8	Daily shift.
III. . . . .	Quan.	No	Yes	2.7	Daily shift.
IV. . . . .	Qual.	Yes	No	4.1	Daily shift.
V. . . . .	Qual.	No	Yes	3.8	Daily shift.
VII. (Normal) .	Qual.	Yes	No	4.2	Daily shift.
IX. . . . .	Quan.	No	Yes	4.6	3 to 4 days.
X. (Case III, 2d admission)	Quan.	No	Yes	3.4	2 days.
XI. . . . .	Quan.	Yes	No	4.2	3 to 5 days.
XII. . . . .	Quan.	Yes	No	4.3	5 days.
XIII. . . . .	Quan.	Yes	No	5.8	5 days or longer.
XV. . . . .	Quan.	Yes	No	5.8	5 days or longer.

In Table I, we have summarized the cases in order to show the ratios of available carbohydrate to fat at which ketone bodies appeared quantitatively or showed a marked qualitative increase in the urine. The formula adopted for the expression of the ratios is:

$$\frac{F}{G} = \frac{\text{gm. fat}}{0.58 \text{ gm. P} + \text{gm. CH}}$$

(F = fat, G = available carbohydrate, P = protein, CH = carbohydrate.) The average value for the ratio at which ketone bodies appeared in the urine by qualitative test (sodium nitroprusside), or showed a definite increase quantitatively, is 4 gm. of fat to 1 gm. of available carbohydrate. This formula makes

no allowance for possible antiketogenic action of fat nor for the possible ketogenic action of protein as do most of the formulæ which have been recently presented. The formula suggested by Shaffer is based on certain assumptions as to the ketogenic and antiketogenic factors of the food elements. The ketogenic factor for protein is based upon the one analysis of ox muscle by Osborn.<sup>6</sup> The variation in the amino-acid content is uncertain, and the ketogenic value of protein is yet to be demonstrated with the same degree of probability as its glucose yielding (antiketogenic) capacity. The antiketogenic factor for fat is based on the still quite debatable question of whether the glyceride of the fatty acid is metabolized in the same manner as glycerol. Lusk<sup>6</sup> states that "Giving fat with meat to a diabetic will not ordinarily increase the sugar in the urine. The writer has never observed such an increase in any of the work of his laboratory. On giving meat in diabetes, the fat metabolism is reduced as it would be in the normal organism, and yet there is no effect on the D:N ratio, and therefore the latter cannot be influenced by the quantity of fat burned." Although the D:N ratio of 3.65 is not conclusively proven, this figure is generally accepted. Shaffer has discussed in detail the ketogenic and antiketogenic factors of metabolized food in several papers. We have reached the conclusion that the formula, as presented above, is an expression, in terms of grams of available carbohydrate and grams of fat, which can be applied more simply in the every-day calculation of diets than most other formulæ, and with equal safety.

We give in detail a portion of the data from Case XV in Table II. Only the periods which are essential for discussion are presented. The patient, a male, aged twenty-five years (height 168.1 cm.; weight, 54 kilos), served with the army in France. He returned apparently in good health. Late in the summer of 1921, he noticed thirst, rapid loss of weight and weakness, for a period of six weeks. He was admitted to the hospital on October 15. The blood sugar was 1.81 mgm. per 100 cc; blood CO<sub>2</sub>, 24.7 vols. per cent. Clinically, he was the picture of acute diabetes. After several days of a reduced diet and starvation, his urine became free from sugar and acetone. The diet was then gradually increased until it proved a maintenance diet. Repeated basal metabolism determinations have shown his rate to be a total of 54 calories per hour, or a variation from normal standard of about -13 per cent. The patient, being an employee of the hospital, returned to his active duties and has coöperated with us with great care and fidelity in all details. His diet has been furnished by the metabolism kitchen of the hospital, the case being carefully followed for over a year. During this period, his weight has been maintained at between 54 and 55 kilos, he has remained sugar free and continued his usual duties. The diet during this period has had an approximate value of basal plus 105 per cent.



TABLE II.

Date.	Carbo- hydrate.	Protein.	Fat.	Urine N.	Total ketone bodies as acetone, gms.	Weight.	Blood sugar, mg. 100 cc.	
$\text{PERIOD II. } \frac{F}{G} = \frac{F}{0.58 P + CH} = \frac{212}{109} = 1.95$								
Feb. 22	80	50	212	8.7	0.365	...	0.91	
23	80	50	212	8.3	0.178			
27	80	50	212	7.5	0.297			
28	80	50	212	6.7	0.206			
Mar. 1	80	50	212	8.0	0.239	54.4	54.6	
2	80	50	212	8.8	0.427			
5	80	50	212	8.2	0.347			
6	80	50	212	8.2	0.347			
7	80	50	212	7.5	0.406			
8	80	50	212	5.3	0.253			
9	80	50	212	7.1	0.376			
				average 7.7				
$\text{PERIOD III. } \frac{F}{G} = \frac{235}{109} = 2.14$								
Mar. 12	80	50	235			54.2	0.90	
13	80	50	235	5.5	0.600			
14	80	50	235	5.6	0.397	...		
15	80	50	235	5.6	0.382			
16	80	50	235	6.5	0.448			
19	80	50	235	4.8	0.535			
20	80	50	235	5.5	0.426	54.2		
				average 5.6				
$\text{PERIOD IV. } \frac{F}{G} = \frac{247}{82} = 3.0$								
Mar. 21	53	50	247	4.7	0.784	54.4	0.93	
22	53	50	247	5.0	0.800			
23	53	50	247	6.1	1.805			
	53	50	247	...	...			
26	53	50	247	4.4	1.580	54.4		
27	53	50	6.7	1.480				
28	53	50	247	6.4	1.300	54.4		
29	53	50	247	5.1	2.250	...		
30	53	50	247	6.9	1.280	54.4		
	53	50	247	...	...			
April 2	53	50	247	6.2	1.670			
3	53	50	247	5.8	2.790	54.2		
4	53	50	247	5.1	1.740			
5	53	50	247	6.8	1.410			
6	53	50	247	6.5	1.610			
7	53	50	247	6.7	1.520	54.3	0.87	
10	53	50	247	average 5.3	...			

TABLE II.—*Continued.*

Date.	Carbo- hydrate.	Protein.	Fat	Urine N.	Total ketone bodies as acetone, gms.	Weight.	Blood sugar, mg. 100 cc.
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$$\text{PERIOD V.} \frac{F}{G} = \frac{264}{46} = 5.74$$

April 13	17	50	264	6.3	4.29	54.4	0.81
14	17	50	264	6.9	3.29		
15	17	50	264	5.5	3.70		
16	17	50	264	5.5	3.70	...	
18	17	50	264	7.4	3.16	56.2	
19	17	50	264	5.6	1.91		
20	17	50	264	6.7	2.50		
24	17	50	264	5.5	1.49		
25	17	50	264	6.6	1.80	54.1	0.92
26	17	50	264	6.7	2.78		
27	17	50	264	8.7	2.21		
May 2	17	50	264				
3	17	50	264	7.6	0.10	54.1	
4	17	50	264	6.9	1.86	...	
8	17	50	264	7.0	1.30	54.3	
9	17	50	264	6.5	1.75		
10	17	50	264	5.1	1.47		
11	17	50	264	7.4	1.85		
12	17	50	264	5.9	1.87	54.3	
14	17	50	264	4.6	2.38		
15	17	50	264	8.4	1.47		
16	17	50	264	7.1	1.37	54.4	
				average 6.6			

$$\text{PERIOD VI.} \frac{F}{G} = 3.0$$

May 17	53	50	247	8.2	1.860		0.95
18	53	50	247	6.6	0.670		
21	53	50	247	5.1	0.460	54.5	
22	53	50	247	4.6			
23	53	50	247	5.4			
24	53	50	247	6.1	0.610	...	
25	53	50	247	6.3	0.620	54.4	
26	53	50	247				
27	53	50	247				
30	53	50	247	5.7	0.410		
31	53	50	247	6.4	0.520		
				average 6.0			

$$\text{PERIOD VII.} \frac{F}{G} = 2.14$$

June 4	80	50	235				0.94
5	80	50	235	...	...	54.2	
6	80	50	235				
7	80	50	235	...	...	...	
8	80	50	235	5.5	0.30		
9	80	50	235	5.5	0.30	54.2	

In considering the estimated values of given diets calculated from Atwater and Bryant's tables, we wish to point out certain facts, and discuss their bearing on the work here presented. We have selected for purposes of illustration the diet given on March 22, in Table II, the only part of the period in which the excretion of ketone bodies increased markedly, and have prepared Table III from Atwater and Bryant's tables, giving minimum, average, and maximum values for the articles of food used this particular day.

TABLE III.

Food.	Grams.	Carbohydrate.			Protein.			Fat.		
		Min.	Ave.	Max.	Min.	Ave.	Max.	Min.	Ave.	Max.
Orange . .	EP 100	11.6	11.6	18.5	0.8	0.8	1.1	0.1	0.2	0.3
Butter . .	80	0.0	0.0	0.0	0.8	0.8	0.8	68.0	68.0	68.0
Cream . .	250	7.5	7.5	7.5	5.5	5.5	5.5	100.0	100.0	100.0
Eggs . .	EP (2) (100)	0.0	0.0	0.0	10.0	13.4	16.0	8.6	10.5	15.1
Bacon . .	EP 50	0.0	0.0	0.0	3.2	5.0	9.0	20.0	33.7	39.9
Ham . .	EP 55	0.0	0.0	0.0	6.6	10.9	12.6	9.5	11.4	31.2
Lettuce . .	EP 50	0.8	1.5	2.5	0.4	0.6	0.9	0.1	0.2	0.3
Rutabaga .	EP 100	6.2	8.5	10.3	0.9	1.3	2.0	0.1	0.2	0.3
Green pepper	EP 50	2.3	2.3	2.5	0.8	0.8	0.8	0.1	0.1	0.1
Cauliflower	AP 50	1.7	2.4	3.0	0.8	0.9	1.0	0.1	0.3	0.4
Tomato . .	AP 50	1.0	2.0	3.3	0.2	0.5	0.7	0.1	0.2	0.7
Sauerkraut .	AP 100	3.3	3.8	4.4	1.5	1.7	1.9	0.2	0.5	0.8
Asparagus .	AP 100	2.2	2.8	4.1	0.9	1.5	2.4	0.0	0.1	0.2
Carrots . .	EP 50	3.3	4.7	6.9	0.4	0.6	1.0	0.0	0.2	0.4
Peas . .	AP 25	1.2	2.5	4.4	0.4	0.9	1.5	0.0	0.1	0.2
Walnuts . .	EP 10	1.3	1.3	1.9	1.4	1.8	2.0	6.0	6.4	6.7
Cream cheese	AP 10	0.1	0.2	0.4	1.8	2.6	3.7	2.5	3.4	4.5
Celery . .	EP 10	0.3	0.3	0.5	0.1	0.1	0.1	0.0	0.0	0.0
Olives . .	EP 10	1.2	1.2	1.2	0.1	0.1	0.1	2.8	2.8	2.8
Oil . .	8	0.0	0.0	0.0	0.0	0.0	0.0	8.0	8.0	8.0
Total . .		44.1	52.6	71.2	36.6	79.8	63.1	226.1	246.3	279.9

For this day (March 22, Table II), the diet desired was one yielding carbohydrate (53 gm.), protein (50 gm.) and fat (247 gm.), which, on the basis of our calculation, gives a carbohydrate-fat ratio of 1 : 3. The average values yield approximately these amounts. Furthermore, it is observed that, although these amounts furnish the carbohydrate-fat ratio desired for the patient within the limitations of our experiment, any other combination of the minimum, average or maximum values shown gives a very different value for the ratio computed by the same formula.

Thus: Min. Ch = 44.1. Average P = 49.8. Max. fat = 279.9. Substituting

$$\frac{\text{Fat}}{0.58 \text{ P} + \text{CH}} = \frac{279.9}{29 + 44.1} = 3.84$$

Using another combination, we have: Max. CH = 71.2.  
Average P = 49.8. Min. fat = 226.1. Substituting

$$\frac{\text{Fat}}{0.58 \text{ P} + \text{CH}} = \frac{226.1}{29 + 71.2} = 2.26$$

Ratios computed by other formulæ would likewise vary. Therefore, it is quite apparent that for any given day, the error may be considerably more than is consistent with the purpose of the experiment.

Although we do not know that Case XV was actually burning 2700 calories per day (which in his case = basal + 105 per cent), he was approximately in nitrogen equilibrium for a period of months, with no significant variation in weight. The nitrogen content of the above diets are: Minimum, 5.86 gm.; average, 7.97 gm.; maximum, 10.1 gm. The patient's nitrogen excretion for the day was 6 gm. (5 + 1 gm. for feces nitrogen). During the whole experiment, the nitrogen excretion varied from 4.4 gm. to 8.7 gm., which, with the addition of 1 gm. for feces nitrogen, makes the total excretion 5.4 gm. to 9.7 gm.; whereas the minimum and maximum variation for food nitrogen, as calculated from Atwater and Bryant's tables, is 5.86 to 10.1 gm. The average calculated nitrogen intake is 8 gm. and the average excretion, plus 1 gm. for feces nitrogen, is approximately the same. However, taking into account these discrepancies on the one hand, and the fact that the body weight was maintained constant over so long a period on the other, we feel justified in concluding that the patient was in food equilibrium. No attempt was made to control the water balance. We have appreciated from the outset the necessity of knowing what foodstuffs are actually burned in the body at the time there is an increase in the production of ketone bodies in order to estimate with even approximate accuracy the carbohydrate-fat ratio. The means for securing data of any great significance have not been available, for the only methods at hand were those used in the determination of basal metabolism and respiratory quotients, clinically.

In the earlier cases (Table I), where daily shifts were made, the ratios were more variable than in the later cases. It became apparent, as our work proceeded, that calculations based upon such short periods were not accurate indications of the actual metabolic conditions, partly, at least, because of this possible error in calculated food values. Therefore, whenever possible, we lengthened the periods of each isodynamic shift. We are convinced that this criticism holds for much of the work on the carbohydrate-fat ratio presented elsewhere.

It is interesting to apply the data presented in Period V of Table II to Shaffer's<sup>4</sup> revised formula. The food fed is 17 gm.

of carbohydrate, 50 gm. of protein and 260 gm. of fat. The urine nitrogen averages 6.6 gm. per day (adding 1 gm. for feces nitrogen = 7.6 gm.). The nitrogen intake averages 8 gm.

$$\frac{(\text{Total calories of energy exchange}) - (100 \times \text{urine N})}{50} = \text{grams}$$

food carbohydrate to provide approximate ketogenic balance, or

$$\frac{2730 - 660}{50} = \frac{2070}{50} = 41$$

or 41 gm. of food carbohydrate must be burned to prevent ketosis. Slight ketosis occurred with only 17 gm. of food carbohydrate.

Calculating the expected ketone excretion, using Shaffer's<sup>4</sup> factors, we have:

		Ketogenic millimols.	Antiketogenic millimols.
Glucose, 17.0 gm.	$\times 5.56$	..	94.6
Urine N, 6.6 gm.	$\times 15.00$	99.1	
	$\times 20.00$	..	132.0
Fat, 264.0 gm.	$\times 3.43$	905.5	
	$\times 0.57$	..	150.5
Total millimols . . . . .		1004.6	377.1

Assuming 1 millimol of antiketogenic substance equivalent to 2 millimols of ketogenic substance, then  $1004.6 - (2 \times 377.1) = 250.6$  excess ketogenic millimols. Expected ketone excretion would be, then,  $250.6 \times 0.104 = 25.2$  gm. ketoacid. However, but 4.29 gm. ketoacid were excreted.

Applied to Woodyatt's formula

$$\frac{\text{FA}}{\text{G}} = \frac{0.46 \text{ P} + 0.9 \text{ F}}{0.58 \text{ P} + \text{CH} + 0.1 \text{ F}} = \frac{23 + 238}{29 + 17 + 26} = \frac{261}{72} = 3.57$$

or a ratio which would lead one to expect a marked ketone body excretion.

Likewise, applying Hubbard's calculations,<sup>10</sup> 264 gm. of fat should yield approximately 250 gm. of fatty acid. With the assumed ratio of 1 mol. glucose to 2 mols. fatty acid, the glycerol of fat should help completely oxidize about one-third, or 84 gm., of this fatty acid. The glucose from protein in excess of that used for the amino-acid ketogenic equivalent of protein would help oxidize  $0.25 \times 50 = 12.5 \times 1.5$  (reducing to terms of fatty acid molecular equivalents)  $\times 2 = 37.5$  gm. of fatty acid. The 17 gm. of food carbohydrate would account for  $17 \times 1.5 \times 2 = 51$  gm. of fatty acid, or  $84 + 37.5 + 51 = 172.5$  gm. of fatty acid. This amount of fatty acid could be accounted for by the anti-ketogenic factors, leaving a balance of  $250 - 172.5 = 77.5$  gm. of fatty acid to be excreted.

**Discussion.** It is apparent, then, that the calculations based upon the assumptions of the authors quoted do not hold for the

case under discussion, nor do they hold for the majority of our cases. This discrepancy between calculated and observed findings is appreciated by these authors.

The point we wish to emphasize is that, although we have no solution for this difficulty in regard to the chemical relationships involved in the ketogenic-antiketogenic ratio, our data tend to show that fat can probably be given to many diabetics in ratios still higher (see Table I) than any yet proposed. And that as yet, the simple gram ratio of available carbohydrate to fat is most satisfactory for practical purposes. One case which has maintained body-weight and preserved a normal blood sugar has been followed for one year on a diet in which the carbohydrate-fat ratio was high.

There have come to light in the study of the subject facts which require special emphasis:

1. We have been able to attain such high ratios only in cases where a relatively high-fat diet has been introduced by gradual increases in the fat, with a correspondingly gradual reduction in the carbohydrate.

2. In severe cases entering the hospital with blood  $\text{CO}_2$  of 25 vol. per cent, or less, we have been unable to give a high ratio carbohydrate-fat diet immediately without a fall in the blood  $\text{CO}_2$  and grave symptoms of acidosis. Our experience has been the same, whether the total calories of the diet given were low or calculated to maintain the patient's metabolism. This observation has led us to question whether there is a difference between the effect of ingested fat and body fat on ketone production. We are not prepared to make further comment on this point at present, beyond the statement that we have accomplished by starvation or low protein and carbohydrate intake what we could not accomplish by diets of greater caloric value regardless of the amount of fat. In other words, we have been able to clear up sugar and acetone excretion more quickly in the majority of cases, without apparent injury to the patient, by undernutrition to the point of starvation. This subject is to be discussed in a subsequent paper. After the patient has been rendered sugar and acetone free, we have gradually increased the fat to a high ratio, which has been maintained for months without apparent deleterious effect upon the patient, although accompanied by a considerable excretion of ketone bodies.

3. If Periods IV and VI, III and VII, Table II, are compared, it is observed that the acetone excretion in the later periods is less, although apparently the same amounts of foodstuffs are being burned. Often when an isodynamic shift is made, there is an increase in the ketone excretion which tends to subside as the period continues. This suggests that certain adjustments in the complete oxidation of fat take place slowly.

4. When complications, such as an acidosis or infection are present, it has been impossible to feed fat in such relatively large amounts.

Our procedure today is to render sugar and acetone free by starvation or undernutrition on a low-protein and carbohydrate diet as formerly, then to increase the fat to a relatively high ratio (usually 3 to 4) in relation to the available carbohydrate, and lastly to work out dietary tolerance by increasing all constituents at intervals of two or four days. Observation of fasting (A.M.) blood-sugar values with each increase provides a valuable check upon the advisability of increase. In milder cases, the blood-sugar may be kept normal and a maintenance diet given, while in the more severe cases, the blood-sugar often rises above normal values without glycosuria, but with the continuance of a maintenance diet. We are faced with the fact that in many severe cases, it is often impossible to render sugar or acetone free, and at the same time provide a maintenance diet. However, high-fat diets have been tolerated after being gradually attained with an increase in the strength and subjective well-being of the patient.

**Summary.** 1. The carbohydrate-fat (antiketogenic-ketogenic) ratio, which leads to an increase in production of ketone bodies, has been determined in 11 cases of diabetes mellitus and 1 normal individual.

2. When the ratio is computed from the carbohydrate in the food plus 58 per cent of the protein in grams and the fat in grams, it is approximately 1:4 in both diabetic and normal subjects. That is,

$$\frac{F}{G} = \frac{\text{gm. fat}}{0.58 \text{ gm. P} + \text{gm. CH}} = \frac{4}{1}$$

3. The difficulties of calculating the antiketogenic-ketogenic ratio upon the more accurate molecular basis suggested by Shaffer is discussed.

4. Briefly, the facts are: (a) Lack of data as to what food elements are being burned by the body; (b) the part fat may take in antiketogenesis; and (c) the role of protein in ketogenesis.

5. The time factor in the adjustment of the body metabolism to changes in the carbohydrate-fat ratio is demonstrated.

6. Attention is called to the error which may occur in the use of tables for calculating food values. We have attempted to minimize the error by observing the effect of the diet over long periods, after making isodynamic shifts in the diet at widely separated intervals. The maintenance of a constant weight and nitrogen equilibrium in these long periods lends support to our opinion that the food taken is approximately the food burned.

7. Relatively large amounts of fat may be used in diabetic

diets without injury to the patient. There are, however, the following qualifications:

(a) We have been able to free the urine from sugar and acetone bodies more quickly by undernutrition to the point of starvation than by any diet where exogenous fat is substituted for the amount of body-fat assumed to be burned.

(b) There is need, as yet, to follow carefully any severe case of diabetes where the ratio is not well within the limits of 1 to 4.

(c) In the presence of infection or an already severe ketonuria, high-fat diets are not advised.

8. Our method of procedure in the dietary treatment of diabetes has been briefly outlined.

**Conclusion.** 1. The carbohydrate-fat ratio, at which the ketone bodies fail to be completely oxidized is apparently fixed, and is the same for both normal and diabetic individuals.

2. For practical purposes, the carbohydrate-fat ratio of 1 : 4, calculated from the formula

$$\frac{F}{G} = \frac{\text{Fat in grams}}{0.58 \text{ gm. P} + \text{gm. CH}}$$

is the most serviceable in the construction of diets where it is desired to obtain a maximum caloric intake with a minimum in the form of carbohydrate.\*

\* We submit these findings in spite of the great advances made in the treatment of diabetes by the brilliant work of Dr. Banting and others, because we feel that adequate dietary control will remain the basis of treatment for many cases, especially those of the milder type. Furthermore, if an extract can enable the body to burn a known amount of carbohydrate, a knowledge of the carbohydrate-fat ratio will enable us to use fat in amounts which will insure the greatest energy possible, especially in the severest cases.

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## A SIMPLE CLASSIFICATION OF LYMPH-GLAND ENLARGEMENTS, BASED UPON GLANDS REMOVED FOR DIAGNOSIS.

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THERE has been no dearth of attempts at the classification of the lymphadenopathies, during the history of their recognition, as more or less definite entities or as conspicuous evidences of deeper and more general disorders. The systems have, however, been based for the most part upon single outstanding features, such as the locality or individual character of the tumors or upon the alterations of the circulating white corpuscles. Constitutional effects, such as anemia or cachexia, have been, by some, included among the criteria for the separation of otherwise similar diseases. As one reviews the history of our knowledge, through the work of such men as Wilkes, Virchow, Kundrat, Trousseau, Reed, Sternberg, Türk, McCallum, Ewing and Webster, there is an evident paucity of criteria upon which a diagnosis can be reached in any given case, especially where one has to do with the zone between true leukemia and sarcoma, conditions which have presented a bewildering number of varieties. There has been too great a tendency to make subdivisions upon the basis of one or two instances which vary in minor factors. Sternberg,<sup>4</sup> in his chapter in Marchand and Krehl's *Handbuch der Allgemeinen Pathologie*, while describing many unusual conditions in beautiful detail, confuses as much as helps by offering so many explanations and possibilities. One also asks, when studying the whole subject, if there be no systematic clinicopathological basis upon which a definite classification can be made. At present, this question must be answered in the negative, especially since no data of dependable worth as to etiology are at hand. Up to about ten years ago the progress depended entirely upon studies of clinical and necroscopical character. Since then, bacteriological and parasitological data have been accumulating, albeit with small definite results, and greater attention has been paid to the bioscopical diagnosis by adenectomy and the results of roentgen-ray treatment. This history having accumulated, it is not without hope that we may look forward to a classification of lymph-gland enlargements which will enable the clinician to apply to a given case some rules for diagnosis, therapy

and prognosis. It is in this direction that we offer the results of our clinical and pathological studies of upward of one hundred cases, an analysis of which, when combined with the experiences given in the literature, has suggested that we venture a classification based upon physical examination and pathology. The very fact that so many classifications have been offered is evidence that no unanimity exists relative to the proportionate value to be given to each of the criteria presented by cases of adenopathy, a state of affairs which throws us back upon a pathological basis. The clinical features are too variable to allow quantitative values to be assigned them so that a mathematical formula, such as is used in botany, cannot be employed unless one had a really enormous number of cases reported in identic manner from which percentage figures could be quoted. Since this does not exist, the adoption of an acceptable pathological classification permits the preparation of a table of a few definite clinical characters and a number of others with a high degree of probable value.

Lymphatic tissue is distributed in the body as illy outlined lymph-cell collections in organs and in the bone-marrow, as solitary and agminated lymph follicles such as exist in the intestinal wall, as lymph nodes, and as the spleen. The first has no special architecture, its elements being only small lymphatic mononuclears closely packed and apposed or separated by delicate fibrils. Solitary and agminated follicles possess an orderly arrangement of central germinal area and a major part consisting of adult lymphocytes. Indefinite cords and sinuses may occupy the spaces between the follicles proper, the whole being surrounded by some condensation of tissue, but not by a marginal sinus and fibrous capsule. Lymph nodes, unlike the foregoing, are accumulations of lymph cells arranged in an apparently purposeful manner and with an architecture of practically identic character throughout the body, varying only in quantitative sense. Whereas they are simple in construction in the intestinal wall, the regional chains and the plexuses around the hilum of viscera are quite definitely arranged, apparently to care for drainage of the area in which they lie. The spleen is, indeed, only a quite complex lymph or hemolymph node, its lymphoid character being supplemented by blood spaces and its activities being more closely associated with the blood than those of its relatives, disseminated lymphatic bodies. The spleen is peculiar also in being often involved in the diseases of lymph nodes, while these latter are not so frequently altered in diseases originating in the larger organ, such as a primary splenomegaly. The features that concern the present study most directly are the elements comprising the lymph node and the architectural relations they bear to one another. Without going too deeply into histology, it is necessary, however, to discuss the units of cellular construction.

There are three elements involved in the make-up of a node, which are peculiar to it—the lymphoid cells, endothelial cells of the sinuses and perivascular spaces and the reticulum cells and fibers. There are constantly present, however, structures which belong to the so-called myeloid series, polynuclear neutrophiles and eosinophiles, and large mononuclears comparable to the formative cells of the bone-marrow and believed to be the forerunners of polynuclear varieties. Some of these three types are doubtless deposited by the circulating blood. Certain observers have wished to see myeloid tissue in lymph nodes, a view which would explain the presence of these cells upon the basis of local production. Since, however, the diseases of lymphatic nodes never express themselves with alteration of myeloid cells but of the lymphoid series, and since myeloid alterations are so definitely associated with bone-marrow changes, it is not necessary to discuss further for our purpose the academic question of the existence normally of differentiated marrow cells in the lymph nodes. When polynuclear cells are present, there is usually other evidence of inflammation and when myelocytes and promyelocytes are found they can be explained by other lesions of bone-marrow disease.

The first essential elements of the lymph nodes are laid down to form groups called follicles, composed of small mononuclears, apparently growing from larger cells of generally similar character which lie in the center of the group. Here also one finds a small bloodvessel with circumferential endothelial cells. The small mononuclears are extended from the follicles in strands or cords, which are separated from one another by spaces—sinuses, lined by cells apparently of the endothelial series, since they behave like such cells. These sinuses have a delicate network of fibers, within which lie mononuclears, polynuclears and red blood cells.

The framework of all these structures is a delicate reticulum, fitted with stellate cells, some of which have a large, almost vesicular nucleus, and a more compact fibrous tissue with elongated nuclei, which seems to emanate from the large trabecula and from the bloodvessels. There is some question as to whether the reticulum can produce all the fibers seen in certain lymphadenopathies, there being the idea in many quarters that the true fibrous tissue of the gland supplies all this. Our own view is that the reticulum is certainly responsible for much of the fibrosis in early Hodgkin's disease since fine fibrosis is found well developed in the follicle when the Reed cells are beginning along its edge. This delicate supporting tissue is more distributed in the gland than is the coarser connective tissue. It is an important part of the minute construction of lymphosarcoma. For these reasons, we shall write of the supporting tissue as reticulum and imply all the fibrous elements of the lymph node.

The bloodvessels do not seem to undergo very specific changes

during the development of pathological lesions in lymph nodes or at least they do not assume any peculiar character indicative of one or another condition. The capsule and larger trabecula, the coarse mainstays of the node, are for the most part passive and, with few exceptions, fail to participate actively in morbid lesions.

The elements that concern the study of lymphadenopathy are, therefore, lymph cells in their peculiar arrangements, endothelial cells and the reticulum to which may be added units not intrinsically part of lymphatic tissue, the myeloid cells.

The material at our disposal for this study consisted of 65 diagnostic adenectomies upon thoroughly studied and tabulated cases, from 5 of which a second gland was also excised, 10 autopsies and 18 partly tabulated cases, from which glands were submitted for study. These pathological preparations were studied according to the type or types of cells that predominated in the process, the relation of these cells to each other and to the normal architecture. From such a study, it developed that certain groups of preparations were formed because of the similarity of cellular components and collections comprising them and because of the retention or destruction of normal architecture. Starting from these groups, we constructed a scheme based upon changes in each one of the component elements of lymphatic tissue accordingly as they were in normal or abnormal number, in normal or abnormal location and arrangement. The behavior of the various elements, described in a general manner in the following paragraph, was actually traced in our preparations and the principles laid down can be applied to any given section.

The particulate unit of lymphatic tissue, the small lymph cell, being most important, changes in its number, type and arrangement are the first considerations. Reduction of the number of these cells is rare and only seen with general atrophy, as in senility. We may dismiss at this point all hypoplasias and atrophies within lymph nodes, since the disappearance of the whole or parts is not common and of no significance in the diseases to be discussed. Some elements, apparently atrophic, may be merely overshadowed by increase of others.

The principal change in the number of lymph cells, an increase or hyperplasia, constitutes the most important single feature in these glands. This may be a simple orderly process with retention of normal relationships or it may be excessive and destructive of architecture. The absolute increase is independent of the proportion of small mononuclears in the cords and outer zones of the follicles to the larger cells in the follicular centers, the so-called lympho-blasts. No definite value of classification can be placed upon the relation of these two forms, except in so far as the follicular architecture is retained or lost. It would seem, however, that in hyperplasia under the influence of acutely or continuously acting

stimuli as in inflammation, the follicular center with its large pale cells and a mononuclear zone of considerable width are retained in recognizable form. Aside from these two types, there is the plasma cell, almost certainly a derivative of the lymphocyte.

Hyperplasia of these elements in orderly arrangement expresses an obvious attempt to retain approximately normal architecture. When the identity of the follicle and cords is lost, it implies that restraint of growth is lost. To the first type of hyperplasia we apply the term "restrained" growth, to the latter "unrestrained" growth. The latter may go on within the confines of the glandular capsule, or it may penetrate the latter. According to the rules of pathology, the malignancy of any excessive growth is directly proportionate to the degree of departure from normal positions and arrangements. So, too, the advent of new forms of cells increases the abnormality and malignancy, using this term as indicative of the inability to return to normality. However, these changes must be not only quantitative and qualitative, but they must be uniform and sustained.

The size of cells of the lymphatic series is of some help in deciding the activity of the process locally, but cannot be used as a final criterion. The adult cells in normal positions are of the usual size of lymphocytes, but this size may be retained when all architecture is lost.

In "restrained" hyperplasia cells of both lymphocytic and lymphoblastic proportions are usually present; but in certain cases of sarcoma we have found areas, in close proximity, made up wholly of large and small cells. Sometimes the large cells approach in size that of endothelial or reticulum cells. Identification has been made by us upon the basis of other cellular relations and the usual staining reactions; the Schridde granule method has failed us entirely.

Alterations in the endothelia follow the lines given for the lymph cells, increase in normal positions or excessive disproportionate multiplication. Their proliferation along sinuses or about blood-vessels may make them conspicuous and confuse the picture, but their relationship with adjacent tissues is not lost. If multiplication be unrestrained, as in endothelioma, the sinus or perivascular space is so distorted and crowded that adjacent tissues are compressed and may lose all identity. Ewing's description and photographs have been exactly duplicated in some of our cases. Certain of the reticulum cells may also either engage in the process or be involved by it and become indistinguishable from endothelia. Giant forms of three, four or more times the size of normal endothelial cells, are occasionally encountered in both normal and abnormal locations; these may be multinucleated and phagocytic.

The supporting tissue, both reticular and fibrous, seems to be susceptible to the same character of change as one can follow in

the foregoing two elements. On some occasions, it would appear that the reticulum is hyperplastic, on others the connective tissue, the former usually giving rise to fine fibrosis at least at first, the latter, to coarse strands. We think that both are involved in general fibroses of lymph nodes, since we have been able to find fibroglia fibrils very early in true Hodgkin's disease. The behavior of the reticulum and connective-tissue cells is, however, important. When undergoing hyperplasia, the nuclei of these cells may swell to very large size and become what is called endothelioid. Such cells are usually laid along fibers or in small bundles; occasionally they seem to lie in lacunæ. On other occasions, spindle cells may be found in small groups or strands, apparently in active growth; such areas give the impression of a malignant change and this, indeed, may at times be actually what is progressing.

Aside from these changes in elements peculiar to lymph nodes, there may be increase of the adventitious myeloid cells either diffusely or in groups. The arrangement of such increase is not significant unless the polynuclears be aggregated into abscesses. Still another new structure may be found in diseased nodes—the foreign body giant cell. Its exact origin is no more settled here than elsewhere, but there is an abundance of the cells reputed to be its forerunners.

As has already been indicated, and repeated here for consecutiveness, the capsule and larger trabeculæ do not seem to participate actively in diseases of lymph nodes, except perhaps in chronic fibrosis, under which condition hyperplasia may be simple and restrained or destructive of architecture; it may also extend to the tissues about the gland. These tissues are secondarily involved in many conditions.

Degenerative lesions in lymphatic nodes are roughly divisible into those due to the disease virus and those the result of restriction of food supply. Their exact character, with the possible exception of caseation, is not peculiar to any of the recognized morbid states and has not served as a reliable criterion for separation. Local degenerations, to which the term necrosis may apply collectively, are common and because they are gross in some instances, fine in others, and both in still others, they have served as minor distinguishing features.

The foregoing explanation of the basic changes in the histology of the lymph nodes illustrates how each one of the structural units may increase independently. If they were to do so consistently and be combined with uniform clinical expressions, classification would not be so difficult. Sometimes homogeneous hyperplasia of one type does occur and is combined with a definite gross pathology and clinical picture. Under such circumstances, the general grouping is simpler than when several structural elements are involved.

TABLE I.—DESCRIPTIVE OF CHARACTER OF CHANGE IN THE LYMPH NODES BASED UPON NAMES AS THEY APPEAR IN GENERAL USE AND FROM WHICH THE FIFTEEN VARIETIES WERE SELECTED AS TYPES.

Character of pathological change.	Clinical character.	Pathological group.	No.	Specific varieties.	Association.
Hyperplasia	Benign	Lymphoma	1	Lymphoma	....
			2	Status lymphaticus	
			3	Lymphadenoma	....
	Malignant	Leukemic	3	Glandular fever (and acute leukemia)	....
			4	Leukemia	With 5.
		5	Aleukemia or generalized lymphomatosis	With 4 and 6.	
		Neoplastic	6	Leukosarcoma	With 5.
			7	Lymphosarcoma	With 10 and 11.
			8	Reticular sarcoma	With 10 and 11.
			9	Endothelioma	....
10	Cellular		With 7 and 8.		
Neo-inflammatory	Malignant	Lympho-granuloma	11	Fibrous	With 7 and 8.
Inflammatory	Benign	Adenitis	12	Simple	....
			13	Purulent	....
			14	Tuberculous	With 11.
			15	Syphilitic	....

TABLE II.—THIS SHOWS THE CHARACTER OF HISTOLOGICAL CHANGE IN EACH OF THE TYPES SHOWN IN TABLE I. PLUS SIGNS INDICATE THE PRESENCE OF THE CHANGE AT THE HEADING OF THE COLUMNS, AS A DISTINCTIVE CHARACTER; NO SIGN MEANS ABSENCE THEREOF. WHEN PLUS AND MINUS SIGNS ARE COMBINED THE UPPER INDICATES THE PRESENCE OR ABSENCE, AS A RULE, THE LOWER AN OCCASIONAL FINDING.

Lymphoid elements.			Endothelial elements.		Reticular elements.			Special features.											
Restrained hyperplasia.	Follicular centers preserved.	Unrestrained hyperplasia.	(a) Within node.	(b) Through capsule.	New types of cells, plasma.	Restrained hyperplasia.	Unrestrained hyperplasia.	Giant forms.	Restrained hyperplasia.	Fine fibrosis.	Coarse fibrosis.	Unrestrained hyperplasia.	Endothelioid types.	Polynuclear neutrophils.	Eosinophiles.	Giant cells, foreign-body type.	Gross necroses.	Fine necroses.	Capsular adhesions.
1 +	+																		
2 +	+																		
3 +	+																		
4	+																		
5	+	+	+																
6	+	+	+																
7	+	+		+					+	+							+	+	+
8	+	+		+	+				+	+	+						+	+	+
9	+						+	+			+	+							
10 +	+							+	+	+	+	+	+	+	+		+	+	+
11 +	+							+	+	+	+	+	+	+	+	+	+	+	+
12 +	+							+	+	+	+	+	+	+	+	+	+	+	+
13 +	+							+	+	+	+	+	+	+	+	+	+	+	+
14 +	+					+	+	+	+	+	+	+	+	+	+	+	+	+	+
15 +	+					+	+	+	+	+	+	+	+	+	+	+	+	+	+

NOTE.—These charts were made to be read directly across the

The cases of pure hyperplasia of the different histological elements have been grouped, and their combinations have been classed as they fell together. In constructing such groups, we have assumed pure hyperplasia as an increase of one or another type of cell, benign when restrained, malignant when unrestrained, and inflammation as a mixture of normal and adventitious elements in attempted normal relations. We have, however, been obliged to recognize that certain cases had inflammatory characters yet with abnormal prominence of certain cells that suggested hyperplasia of a disorderly variety; to this group, we have applied the term neo-inflammatory, because it had characters like neoplasms yet was histologically inflammatory also. Curiously enough, this is lymphogranuloma or Hodgkin's disease, long considered by some observers to be tumorous.

To summarize thus far, it may be stated that our material was studied from the standpoint of the histological elements responsible for the enlargement of the lymph nodes and that it is possible to find examples among the diagnostically removed tissue wherein this enlargement was due to hyperplasia of each one of the tissue

TABLE III.—THIS SHOWS THE CLINICAL AND GROSS PATHOLOGICAL FINDINGS IN THE TYPES SHOWN IN TABLE I. SIGNS DIFFERENT FROM TABLE II. PLUS AND MINUS SIGNS INDICATE RESPECTIVELY PRESENCE AND ABSENCE OF FEATURE AT HEAD OF COLUMN. NO SIGN MEANS ABSENCE OR INADEQUACY OF INFORMATION. COMBINED SIGNS MEAN THAT UPPER IS THE RULE, THE LOWER OCCASIONALLY HOLDING GOOD.

Clinical Characters.													Gross pathological characters.					
Local.	General.	Separate units.	Coherent or coalescing.	Rapid growth.	Slow growth.	Mediastinum involved.	Cachexia.	Softening of tumor masses.	Enlarged spleen.	Circulating lymphoids increased.	Circulating myeloids increased.	Cutaneous lesions.	One principal tumor.	Massed glands.	Single glands.	Visceral infiltrates.	Visceral tumors.	Bone-marrow specifically involved.
1	+	+		+														
2	+	+		+														
3	+	+		+														
4	+	+		+														
5	+	+		+														
6	+	+		+														
7	+	+		+														
8	+	+		+														
9	+	+		+														
10	+	+		+														
11	+	+		+														
12	+	+		+														
13	+	+		+														
14	+	+		+														
15	+	+		+														

lines, but because of their size, could not be set upon one page.



components, in normal or abnormal relations, as a pure and single type of cellular increase or as a mixed hyperplasia made up of several types. The cases presenting a pure type of hyperplasia of each cell were put into groups and combined hyperplasias were grouped as they fell into combination. When the findings were tabulated, Table II, they were found to correspond with the theoretical classification, Table I.

Having arrived at this stage of our work, the names of all diseases of the lymphoid organs as written in books were copied, the total amounting to nearly fifty, from which, by the elimination of undoubted synonyms and meaningless terms, we made a condensed list of twenty-seven. From these we selected fifteen, which we believed to be separate clinicopathological types, between which there were sufficient differences to be distinctive.

These types were made into a table of clinical characteristics, according to our own records and from the literature. The headings of symptoms and signs amounted to about fifty, but from these 13 were selected as being most definite in their informative quality; this group of 13 will be found in Table III. However, the physical signs and symptoms are so variable that very few of them are of final dependability; many have to be noted as both present or absent. The diagnosis of a given case may, up to a certain point, be made by comparing the data with such a chart, but in closely similar clinical pictures the differentiation must be made by diagnostic adenectomy or on the basis of gross pathology. The tables given here are the result of many larger and more elaborate predecessors. That descriptive of the histological changes, Table II, was made first and then fitted with Table I, which is based upon the names of adenopathy given in the literature but selected as representative separate types. Descriptive legends accompany the tables.

Table I has as its first divisions hyperplasia, neo-inflammation and inflammation. Hyperplasia may be benign or malignant, a character perceived equally in clinical course and by histological examination of the tissue when viewed by the criteria discussed in the foregoing pages. Where inflammation is combined with progressive growth, cachexia and with the increase of certain cells beyond their normal position within the node, the whole process tends toward malignancy; such is the condition in lymphogranuloma. Inflammation is benign clinically and in its attempted retention of normal anatomical characters.

Examination of the pathological characters naturally follows the division of clinical behavior. Hyperplasia of lymphoid tissue has long been called lymphoma so that the term is retained, but simple orderly increases of small mononuclears are not necessarily neoplastic. However, this type of hyperplasia does occur in iso-

lated glands, as local tumefactions and as a general process. When intraglandular hyperplasia becomes so excessive that mononuclears are spilled into the blood stream, the process becomes leukemia. Certain cases have a generalized leukemic pathology, yet do not show increased circulating lymphocytes, aleukemic varieties or phases. Hyperplasia of an exaggerated disorderly kind may occur in restricted localities, assuming then a form comparable to tumors; they may be associated with leukemia or free of this character. All these foregoing forms are strictly of lymphocyte origin. In the true sarcomata of lymph nodes, an increase of more than one element is found, both lymph cells and reticulum being hyperplastic. Under these conditions, the trend is away from purity of hyperplasia, but one or another element always dominates the picture. The next group, lymphogranuloma, combines hyperplasia of certain elements, endothelial cells notably, in atypical arrangement, with the addition of pathological anatomy of chronic inflammation, a construction peculiar to lymphatic bodies. Adenitis exists when all elements of nodal architecture are active and are joined by the adventitious cells of the blood. The next column of numbers is added merely for convenience.

The specific varieties used to illustrate the types of change were selected from the list of pathological states, as mentioned above, and because they are believed to be all the principal kinds of lymphadenopathy. There are doubtless gradations between these individuals; there certainly must be between the sarcomata, for now and again one will find a case that will not permit of this nomenclature. Many varieties of lymphosarcoma have been described, notable among which are chlorosarcoma and plasmocytoma.

Lymphoma is intended to cover the hyperplasias left after certain longstanding irritations and in the condition known as the thymicolymphatic state. Lymphadenoma is a term long used to describe many lymph-node enlargements, but we wish to limit its use and to explain here our reason. The term should mean a tumor of lymph nodes, one made up of and like lymph nodes, with their peculiar construction. Other tumors of the nodes soon lose their architecture and are given appropriate names. We have observed what seems to be correctly called lymphadenoma. A man, aged forty years, was struck in the neck by a baseball, following which, three months later, a large nodular tumor developed at the place of injury. No other lymph-node enlargements existed and the man had a healthy mouth without obvious bad teeth. At operation a compound nodal tumor was removed, the micro-anatomy of which was that of normal lymph node. One year later, when last heard from, he was in perfect health and without a trace of return or extension.

Glandular fever is peculiar in that its acute manifestations are unlike any other condition in the list. It might be related with acute leukemia, which condition may be said to form a connecting link with it and the next disease, leukemia. A diagnosis of acute leukemia has been seriously considered in certain cases of glandular fever. The fever is not included in the tabulation because of the inconspicuousness of the glandular features and ease with which the disease can be separated from the definite lymphadenopathies.

Leukemia proper is self-explanatory. Aleukemic leukemia is the term we apply to pseudoleukemia of Cohnheim, because it is pathologically like leukemia and only separated from it clinically by the inconstancy of hyperlymphocytosis. Ewing's<sup>1</sup> term, systemic lymphomatosis, is satisfactory, but fails to convey the suggestion that the process is histologically like leukemic hyperplasia and that the disease may have phases in which the circulating mononuclears are increased. Leukosarcoma is, according to Sternberg,<sup>4</sup> who first described it, a local leukemic tumor with increased circulatory mononuclears. The typical lymphosarcoma of Kundrat is a mononuclear cell tumor, with fine reticulum and no change in the blood picture. Sarcoma, arising from reticulum or connective-tissue cells, may be either of the round or spindle-cell variety, and when studied microscopically fails to show the purity of the component cells characteristic of sarcomata arising from lymph cells; variability in the size, shape and arrangement of cells is quite typical of these tumors. Endothelioma presents no features of lymphoid tissue within the neoplastic areas, being constructed throughout upon the basis of large cells with loose nuclei.

Hodgkin's disease may be divided into the cellular and fibrous varieties, but whether these are strictly different or only stages of the course of disease is as yet unsettled. We believe we shall be able at a later time to show their individuality (see Ziegler).<sup>8</sup>

The types of adenitis listed in the table are clinically and etiologically different, but analysis by the criteria already discussed does not serve to separate them very sharply.

The column of association is meant to indicate how these various individual conditions are related to one another or how they may transmute. The relation of leukemia and aleukemic leukemia has already been discussed, as has their connection with leukosarcoma. The association of sarcoma with Hodgkin's disease is credited by Ewing<sup>1</sup> upon the basis of work of Welch, Karsner and Yamasaki; we have not had occasion to see it. Lymphogranuloma and tuberculosis are noted as related to one another in deference to the opinion of many writers; our tests have failed to establish the tuberculous basis of Hodgkin's disease.

Having disposed of the groupings in Table I, we may now see how they will fit into the classification from the standpoint of

changes in the histological elements on Table II. The tabulation is made according to the changes described as taking place in lymphoid, in endothelioid and in reticular elements with the addition of special features, such as myeloid cells, giant cells and necroses. A survey of the whole chart reveals at once that there are rough groupings which correspond with the grosser subdivisions of the theoretical and clinical sections. The purity of the first and second gross subdivision is carried forward and is consistent in nearly every particular. When one reviews the neoplastic division, it is evident that more kinds of tissue are involved and that the four specified varieties fall into three general groups. The first embraces the two sarcomata from lymphoid cells (Nos. 6 and 7), the second is represented by reticulum sarcoma and the third by endothelioma alone.

Inspection of the tabulated histological characters of lymphogranuloma reveals that they are distinct from the foregoing varieties, but possess much in common with definite inflammations in the next subdivision. These latter are not greatly different, except the syphilitic, and, indeed, their variations may probably all be explained upon the basis of chronicity.

Section III of the table is an analysis of the clinical and gross pathological features considered to be most distinctive of these lymphadenopathies and most helpful in diagnosis. The twenty headings are selected from seventy tabulated on a large table. However, these are not all of equal value and do not individually possess the same relative value down the list of fifteen specific varieties. Conspicuous in this inconsistency is the rate of growth. What would be rapid for Hodgkin's disease would be slow for purulent adenitis; a rapidly developing sarcoma would be slow for glandular fever. Yet, it is necessary to contrast aleukemic leukemia and leukosarcoma, reticulum sarcoma and endothelioma, acute and chronic Hodgkin's disease. We wish it known that this has but a relative value and that we are aware of it. Many of these features are variable enough in a clinical case to require both a positive and negative sign to indicate that they may or may not be present. The order in which they are placed is that of greatest percentage of positive characteristics. Some of the diagnoses exhibit features requiring a positive entry in two opposed characters. The relative importance of each of these criteria is impossible to evaluate at present because there is no uniformity with which each of the varieties display their special characters as indicated by so many plus-minus signs, and because there is no unanimity of opinion as to the most important ones. These remarks will be emphasized by a review of the table of clinical characters in which it will be seen that no distinct grouping occurs as could be found in the histological analysis. There is a rough grouping of the benign and leukemic hyperplasias and of the small

mononuclear neoplasms, but distinctive subdivisions do not appear. The most important features we believe to be whether the growth is local or general, whether separate or coalescing, whether the spleen is enlarged or not and the state of the circulating leukocytes. The table serves to show that, up to a certain point, a diagnosis may be approximated, but that the settlement of the question must remain for gross or microscopic anatomy to settle. This is especially true of the aleukemic leukemias, neoplasms and granulomata.

Gross pathology, as seen by operative removal of a tumor or at autopsy, is of some value. Or this gross pathology may be discovered by clinical means, among which the roentgen ray is included. Thereby it may be established that the cervical or axillary mass is solitary, a discovery favoring the lymphoid and reticular sarcomata. Like the clinical data, these features in gross pathology have a relative value and are to be used in combination with bedside information. The most important at autopsy would seem to be the existence of a single tumor, the presence of visceral infiltrations and the changes in the bone-marrow. When organs contain infiltrates, it would seem to indicate that the cells of the original process are circulating, or that the visceral nodes have been stimulated to hyperplasia.

Having presented the data acquired by a study of lymph nodes excised during life from cases of lymphadenopathy, combined with an analysis of their clinical character, and having described a theoretical system based upon what is believed can happen in the anatomical elements of lymphatic tissues in terms of the names applied clinically and pathologically, it seems well at this point to define clearly the meaning and limits of each one of the fifteen types we believe to be separate.

The term lymphoma indicates a tumor of lymph cells. The name is retained because of general use, but is restricted in our work to pure orderly hyperplasias, such as are seen in chronic intoxication and in the lymphatic status. Exemplifying the former of these conditions, may be cited the lymphatic enlargements accompanying toxic goiters. This whole conception implies either a local or general increase of discrete glands or of visceral lymphoid collections without distinctive lymphocytosis. The purity of lymphatic hyperplasia in this first group and in the third, the acute forms behaving like acute infectious diseases, is the dominant pathological feature. Glandular fever is, however, combined with a definite circulating mononucleosis. It forms the first of the hyperplasias that seem to be peculiar and restricted to lymphatic tissues and merges with acute leukemia into a group connecting with the chronic form. As a clinical feature, lymph-nodal enlargement is definitely less conspicuous than it is in long-standing diseases, and there is an increase of circulating lymphoid

cells. Lymphadenoma, a compound tumor retaining nodal architecture, must be a rare condition; our case has been cited.

Leukemia is a condition diagnosed clinically by the discovery of an increase of circulating mononuclears. It is a systemic disease characterized by generalized lymph-node enlargement, mononuclear infiltrates in viscera, single or massed glandular tumors usually however, retaining, when *en masse*, their individual outlines. The disease is essentially slow in course and marked by irregular remissions. The spleen is usually enlarged. Histologically, the hyperplasia is pure in type and, although in the late stages destructive of intraglandular architecture, does not involve the capsule and adjacent tissues. Aleukemic leukemia or systemic lymphomatosis is exactly the same process, beginning more insidiously and not associated with leukemic blood. There may be subleukemic phases, however, especially just ante mortem (Sternberg).

Leukosarcoma is defined by Sternberg as a local invasive tumor composed of lymphoid cells associated with a definite but not constant mononucleosis. The fact that it is primarily local differentiates it from the foregoing two varieties. It may become generalized as a late development.

Lymphosarcoma is primarily a local tumor, practically always disseminated before death. The variety found in the intestinal wall may remain local and be amenable to surgical treatment. This tumor differs from leukosarcoma in the absence of circulating mononucleosis, the implication of both lymphoid and reticulum cells, the presence of a fine intercellular fibrosis and a tendency for gross and fine necroses to appear. It was attempted to discover from our sections distinct differences in the vascular supply to account for these necroses, but no result could be achieved.

Endothelioma may be a local tumor or the growth may involve many glands, which, however, tend to remain discrete. The chronicity of the tumor is a marked character. Visceral involvement is rare. Histologically, the peculiarity of the growth lies in the development of islands or strands of endothelial cells, sometimes growing through lymphoid tissues, sometimes surrounded by non-specific fibrous tissue which is disorderly in arrangement.

Lymphogranuloma, or Hodgkin's disease, although usually expressing itself as a local growth, must nowadays be considered as a systemic affection. It can be defined as an enlargement of lymph nodes occurring most often in young adults and adolescents, without mononucleosis, but often in the early stages with polynucleosis, with involvement of the spleen, with a tendency for internal masses to develop, and with a histological lesion, consisting chiefly of inflammatory changes combined with a prominence of large mononuclears suggesting unrestrained neoplastic activity. Its varieties depend upon whether the glands remain isolated or

grow into coalesced tumor masses; the rate of growth, this being more rapid with discrete nodes; the degree of fibrosis, which is greater in the tumor-forming type; the presence of foreign body giant cells and gross necroses, both of which are usually absent from isolated, discrete nodes and present in large fibrous tumors. Large mononuclears, with one compound nucleus or with numerous nuclei, those arranged parallel to the cell wall, are strongly supportive of this growth. Langhans giant cells are occasionally but not necessarily present; they are much more directly indicative of tuberculous adenitis.

Adenitis is that state of lymphatic tissue change in which all elements, normal and adventitious, participate in the process. Its varieties, as noted in Nos. 12 to 15 inclusive, depend upon the nature of the cause and upon the prominence of certain incidental factors. They vary also in terms of chronicity. The simple form differs from the purulent in the rate of growth, the degenerations and the prominence of polynuclears. Tuberculous adenitis need confuse only in respect to Hodgkin's disease, with which it has many similarities. The variety of the latter ascribed to tuberculosis by Sternberg cannot always be differentiated by histology, and a decision must be left to bacteriology. Ordinary cases of tuberculosis are to be distinguished from non-tuberculous lymphogranuloma by the evident attempt at the retention of architecture, the formation of tubercles or at least of foreign body giant cells in granulation tissue and the inconspicuousness of the so-called Reed cells in the variety certainly due to the *Bacillus tuberculosis*.

The small, isolated, firm, slowly growing glands in the adenitis of syphilis are noteworthy for the dense packing of lymphocytes in approximately normal relations and the fine perifollicular and perivascular fibrosis. Gummata may be present.

**Summary.** The study of the material upon which we have worked, especially the anatomy of excised lymph nodes, permits a grouping of cases based upon the type of cell primarily responsible for the enlargement. The groups into which the cases fall correspond first to a theoretical system, based upon what is possible when the component parts of lymphatic tissue become hyperplastic, and second, to types of pathological characters and clinical behavior. Such a classification, although founded upon work which has adduced no essentially new facts, establishes more firmly the nature of lymphadenopathies, since it is based upon tissues removed during life—therefore, during the natural activity of the morbid process. It may help to formulate a simpler scheme for these illy understood entities, and to reduce the number of terms employed in describing them. No system can reach all variants from a type, especially in these diseases where so many confusing individual cases appear. The work also illustrates that certain of the leukemic and neoplastic forms of lymphadenopathy cannot be diagnosed solely upon

clinical signs, but that data acquired by adenectomy must be available for this purpose.

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## A CONTRIBUTION TO THE PHYSIOLOGY OF THE PINEAL BODY.

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THE problem concerning the function of the pineal body is not yet definitely decided. The importance of the pineal body is, however, clear from the fact that its tumor is often attended by "pineal disorder," namely premature development of primary and secondary sexual characters.

**A Historical Review of Experimental Results.** Howell,<sup>24</sup> the first to try the intravenous injection of pineal extract, records that its effect upon the blood-pressure is inconstant. Von Cyon<sup>9</sup> believes, as a consequence of the intravenous injection of pineal extract and of electrical stimulations, that the pineal body plays a role in preserving certain inorganic substances as organic compounds, and moreover, that it regulates the flow or cerebrospinal fluid in the third ventricle. In 1909 Dixon and Halliburton<sup>12</sup> examined the effect of pineal extract, but their results were negative so far as the blood-pressure, heart rate, respiration, the volume of the intestine, kidney and urine secretions are concerned. Jordan and Eyster<sup>23</sup> observed transitory diuresis and glycosuria after the injection of the pineal extract; and Otto and Scott<sup>40</sup> report similar results. Horrax<sup>25</sup> states that intravenous injections of pineal extract would cause a constant but slight fall in blood-pressure.

According to Dana and Berkley,<sup>10</sup> as well as to McCord,<sup>33</sup> a prolonged administration of the pineal drug brings on a relatively rapid growth of the animals subjected to the experiments. Although no serious effects were observed in the animals subjected to the



administration of the pineal drug, the extirpation of the pineal body caused striking results.

Biedl<sup>6</sup> and Dandy<sup>11</sup> subjected dogs, and Exner and Boesse,<sup>14</sup> rabbits, to pinealectomy, but they obtained no affirmative results. On the other hand Sarteschi<sup>44</sup> succeeded in getting positive results after pinealectomy. In 1913, he recorded that guinea-pigs and puppies subjected to the operation revealed an increase in body weight and in the size of the testes, but no change in the other endocrine glands. In papers by Foa<sup>16</sup> we find that pinealectomized cocks showed a hastened maturity and crowed earlier than controls. Besides he observed a marked hypertrophy of the comb and testes in the cocks that were operated on, there was no change in the case of hens. The fact that pinealectomized rats showed an increase in weight of the testes was also recorded by him. These observations were on the whole affirmed by Zoia.<sup>52</sup> Recently Horrax<sup>26</sup> has obtained remarkable results after pinealectomy in many guinea-pigs and rats. His conclusions are as follows: "Pinealectomized male guinea-pigs showed a hastened development of the sexual organs, manifested before maturity by a relative increase in size and weight, both of testes and seminal vesicles, over control pigs of the same litter. Histologically the testes and seminal vesicles of these animals, if taken before the age of sexual maturity, showed a more advanced physiological state than controls.

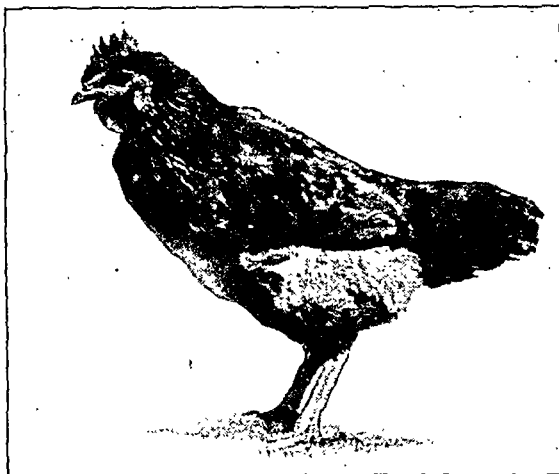
Pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight."

Therefore it appears to be established that in pinealectomized young males the body weight and the size of the testes (in the case of cocks, the combs, and in the case of guinea-pigs, the seminal vesicles also), grow much more rapidly than in control animals. On the contrary no considerable change has been reported as yet in the case of females.

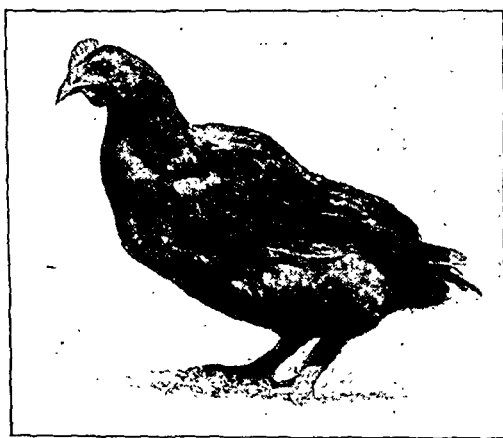
In order to ascertain the function of the pineal body, both in young males and young females, I have undertaken the extirpation of the pineal bodies in many chickens, males as well as females. In all, I performed the operation of pinealectomy on 36 chickens ranging from four to five weeks of age. Besides these chickens 11 others of the same age and weight as those operated on were used for comparison.

**Method of Operation.** The operation was conducted with careful aseptic precautions. The unanesthetized animal was wrapped with sterile gauze, and after shaving and applying of tincture of iodine, the skin on the posterior end of the skull was cut along the median line. Then the bone was so far removed as to allow the exposure of the posterior portion of the superior longitudinal sinus, where two lateral sinuses join. After a transverse section of this portion of the sinus had been made with small scissors, without ligating it, the under stump of the sinus wall was drawn out, which

manipulation permitted an exposure of the pineal body. This was grasped firmly with a small pair of forceps and gently pulled out, caution being taken not to snap it in two but to remove it whole. After the extraction of the organ, which was accompanied by a somewhat serious hemorrhage from the sinus, the wound was closed by suture of the skin. In the control animals also, the skull was opened in like manner, but the wound was immediately closed without opening up the dura mater.



A



B

FIG. 1.—Cocks (Case I), aged two hundred and ten days, one hundred and eighty-two days after operation. A, pinealectomized cock; B, control.

**Postoperative Observations.** Most of the pinealectomized chickens died shortly after the operation from intracranial hemorrhage. Only 4 (3 males and 1 female) survived the operation for any length of time. These were fed under the same conditions as the

control animals and the effects observed. Compared with the control chickens, the pinealectomized animals showed a retarded growth for a few weeks following the operation, but about a month later they began to grow more rapidly than the controls (with the exception of 1 male chicken in which the pineal body had not been entirely removed, as was revealed by the autopsy that was



A



B

FIG. 2.—Cocks (Case II), aged two hundred and fifty-one days; two hundred and twenty days after operation. A, pinealectomized cock; B, control.

made later). Their body weight became greater and their legs longer than in the case of the controls (Figs. 1 and 2). In the 2 males whose pineal bodies were completely removed, the rapid development of the comb and the premature crow deserve special attention and they gave evidence of sexual instinct from thirty-one to fifty days before their controls. (See Table I.)

**Autopsy Findings and Histological Examinations.** Of the animals that survived, the pineal body was completely removed in 3 chickens, 2 males and 1 female, as the autopsy testified. One of the males lived one hundred and eighty-two days, the second two hundred and twenty days, and the third one hundred and thirty days after the operation, whereupon all of them were killed, together with the controls. After weighing or measuring, the endocrine organs were fixed with formalin and sections of them stained with eosin-hematoxylin.

TABLE I.

	Case I (♂)		Case II (♂)		Case III (♀)	
	Pinelectomized chicken.	Control.	Pinelectomized chicken.	Control.	Pinelectomized chicken.	Control.
Age of animal on day of operation in days . . . . .	28	28	31	31	35	35
On the day of killing the animal:						
Age in days . . . . .	210	210	251	251	165	165
Body weight in gm. . . . .	1820	1200	1950	1600	1400	1050
Weight of testes in gm. . . . .	14.3	1.49	18.0	7.0		
Relative weight of testes in gm. to a kg. of body weight . . . . .	7.85	1.24	9.7	4.3		
Weight of ovary in gm. . . . .	...	...	...	...	1.12	0.5
Length of Fallopian tube in cm. . . . .	...	...	...	...	16.0	9.0
Weight of comb in gm. . . . .	5.0	0.7	16.0	2.5		
Weight of hypophysis in gm. . . . .	0.012	0.015	0.012	0.013	0.01	0.0085
Relative weight in gm. to a kg. of body weight . . . . .	0.0060	0.0125	0.0061	0.0081	0.0071	0.0080
Weight of parathyroids in gm. . . . .	0.0078	0.0078	0.0090	0.0110	0.020	0.015
Relative weight in gm. to a kg. of body weight . . . . .	0.0042	0.0058	0.0046	0.0058	0.0142	0.0141
Weight of thyroid in gm. . . . .	0.09	0.065	0.1	0.085	0.12	0.05
Relative weight in gm. to a kg. of body weight . . . . .	0.049	0.054	0.051	0.053	0.085	0.042
Weight of suprarenal in gm. . . . .	0.16	0.182	0.15	0.135	0.135	0.085
Relative weight in gm. to a kg. of body weight . . . . .	0.081	0.151	0.077	0.084	0.096	0.081
Weight of thymus in gm. . . . .	2.75	1.7	3.1	2.7	1.85	1.9
Relative weight in gm. to a kg. of body weight . . . . .	1.51	1.41	1.58	1.7	1.32	1.89
Weight of pancreas in gm. . . . .	3.1	3.25	4.0	3.8	2.8	2.82
Relative weight in gm. to a kg. of body weight . . . . .	1.70	2.7	2.0	2.3	2.0	2.08
Weight of bursa fabricii. . . . .	2.10	2.0	1.8	1.9	1.5	1.7
Length of left femur in cm. . . . .	10	9	11	9	8.0	8.0
Length of left tibio-tarsus in cm. . . . .	13	10.5	14	11	9.0	8.5
Length of left tarso-metatarsus in cm. . . . .	11	9	12	10	8.5	7.9
Age of animal on the day when it crowed the first time, in days	185	*	205	240		

\* Never crowed.

As seen in Table I, the development of the sexual organs (testes, ovary, and Fallopian tube) of the pinealectomized animals was most remarkable, as compared with the controls (Figs. 3 to 5). In the long Fallopian tube the voluminous ampullary part was sharply



FIG. 3.—Testes of the cocks belonging to Case I. The left, those of the pinealectomized animal; the right, those of the control. *a*, testes; *b*, bursa fabricii.



FIG. 4.—Testes of the cocks belonging to Case II. The upper, those of the pinealectomized cock; the lower, those of the control.

contrasted with the slender upper portion, while the same tube in the control is not only short but uniformly slender through its whole length (Fig. 5).

Microscopically, the seminiferous tubules were markedly dilated and contained several layers of epithelial cells showing all stages of spermatogenesis (Fig. 6, A). On the other hand those of the controls remained small and were almost filled with a few layers of not yet differentiated epithelium cells (Fig. 6, B).

With regard to the interstitial cells of the testes, they seemed somewhat increased in number in the pinealectomized animals.

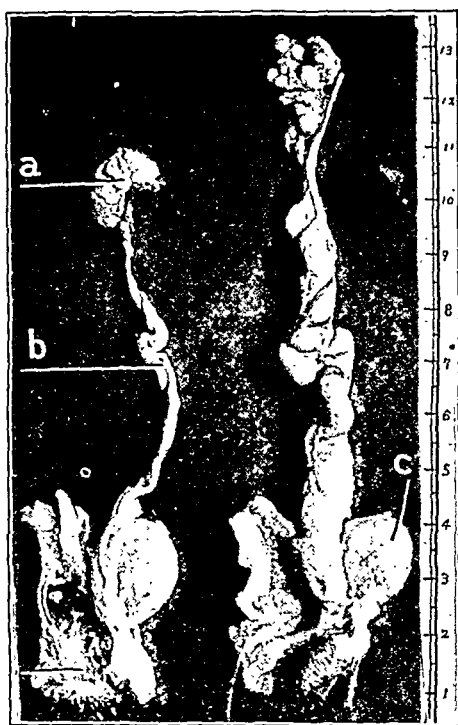


FIG. 5.—Sexual organs of hens, aged twenty-three weeks, one hundred and fifty days after operation (Case III). Right, those of the pinealectomized hen; left those of the control. *a*, ovary; *b*, Fallopian tube; *c*, bursa fabricii.

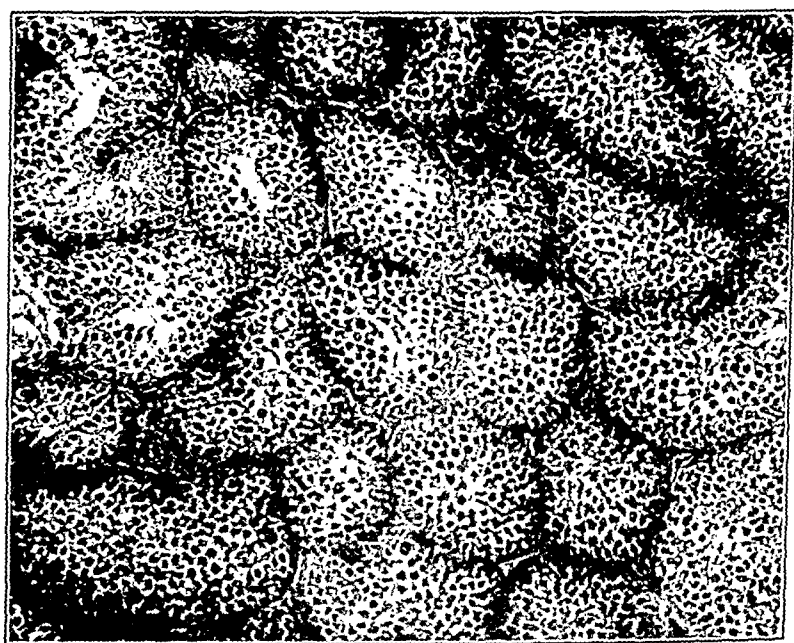
In the section of ovary of the pinealectomized female, well developed follicles measuring more than  $390\mu$  were often met with, some of them projecting above the surface of the ovary, while the same organ of the control contained no such follicle, the largest being less than  $100\mu$  (compare Fig. 5).

As to the other endocrine organs, it may be said that the difference between the pinealectomized and control animals was slight or entirely absent.

The pituitary bodies of the pinealectomized chickens remained normal, so far as their weight, size and structure were concerned,



A



B

FIG. 6.—Sections through the testes of the cocks belonging to Case I. *A*, from the pinealectomized cock; *B*, from the control.

with the exception of Case I, where the gland of the pinealectomized animal seemed to contain more numerous eosinophile cells in the anterior lobe of the organ, than those of the control. Also, the thyroids of the pinealectomized chickens were generally a little heavier than those of the controls. Histologically the vesicles were lined with cubical or columnar epithelium cells and were distended and contained much colloid substance, while those of the controls were lined with flattened cells and remained small. With regard to the adrenal gland, in which the medullary and cortical elements were intermixed and formed columnar groups of cells, there was no clear distinction to be observed between the pinealectomized and the control animals, although the former seemed to possess slightly enlarged cell columns. Other endocrine organs, such as the parathyroids, thymus and pancreas, revealed no peculiar condition either macroscopically or microscopically, in the test animals. The same thing can be said regarding the bursa fabricii.

**Discussion.** With respect to the male chickens, my results coincide with those of Foa and Zoia exactly, but concerning the female chickens the two authors state no change is to be observed as a result of pinealectomy. While Sarteschi reports that the pinealectomized females dislike copulation, Horrax says on the contrary in regard to guinea-pigs: "Pinealectomized females appear to show a tendency to breed earlier than controls of the same age and weight."

Under these circumstances I lay stress on the finding in the case of the pinealectomized female chicken, namely a premature development of the sexual organs. Although the case is only a single one, the finding is so remarkable (see Fig. 5), that there remains little doubt of the fact that the pineal body acts as an inhibitory organ upon the sexual apparatus to young female animals as well as in the males.

Concerning tumors, of the pineal body there are about 90 cases reported, so far as I know; but only 27 of them are cases occurring before puberty. Only 14 of these cases showed the pineal disorder, (Oestreich-Slawyk,<sup>38</sup> Frankl-Hochwart,<sup>17</sup> Ogle,<sup>39</sup> Nagayo,<sup>35</sup> v. d. Bergh,<sup>23</sup> Boehm,<sup>7</sup> Gutzeit,<sup>22</sup> Odermatt,<sup>37</sup> Raymond-Claude,<sup>42</sup> Bailey-Jelliffe,<sup>4</sup> Horrax,<sup>26</sup> Goldzieher,<sup>21</sup> Takeya,<sup>47</sup> Holzhauer<sup>25</sup>); the others revealing no symptoms of sexual prematurity (Schearer,<sup>45</sup> Williamson,<sup>50</sup> Rydinger,<sup>43</sup> Lord,<sup>32</sup> Marburg,<sup>34</sup> Weigert,<sup>49</sup> Falkson,<sup>15</sup> Coats,<sup>8</sup> Gauderer,<sup>19</sup> Zenner,<sup>51</sup> Hoesslin,<sup>24</sup> Laurence,<sup>30</sup> Newmann,<sup>36</sup> Pappenheimer,<sup>41</sup> Garrod,<sup>18</sup> Giebel<sup>20</sup>). The existence of these negative cases, however, does not prove the uninhibitory function of the pineal body in sexual development, for the pineal disorder would appear only when the other endocrine organs could not compensate for the loss of the pineal body.



In this connection it is interesting to refer to a case of hyper-pinealism which Prof. Kosaka\* kindly permits me to quote.

It concerns a man aged twenty-one years and four months, who died of tubercle of lungs and ribs. In spite of his age he seemed like a boy of only about thirteen years. There were no pubic hairs, the penis remained very small, the testes being only 1.5 cm., in length, 1.0 cm. in breadth and 0.9 cm. in thickness. The development of the bones was very much retarded, so that a part of the skull still retained a membranous state. As regards the pituitary body, thyroid gland, parathyroids, adrenals and pancreas, nothing particular was observed, only the pineal body showing a relatively strong development, its transverse diameter being 9 mm. and sagittal length 8 mm. Histologically it had a structure resembling that of a baby's pineal body, the poorly cellulated lymph sinus-like portion remaining remarkably well-preserved, and the trabeculae of the connective tissue scanty. This case indeed affords another proof of the abovementioned statement concerning the function of the pineal body. Nevertheless it appears somewhat strange that the above quoted 12 positive cases, and the case of Kosaka should all belong to the male sex, while no similar cases are known in women, with the exception of 1 reported by Askanazy and Brock.<sup>2</sup>

According to these authors an idiot woman, who died of an epileptiform fit at the age of twenty-three years, had shown a premature development of sexual character. When she was only ten years old the mammae became considerably enlarged, at the age of eleven the pubic hair appeared, and two years later she experienced menstruation. At autopsy the pineal body was found as a very rudimentary organ, its weight being only 0.04 gm., its length 3 mm. and its breadth 2 mm. The other endocrine organs revealed nothing uncommon except the thyroid gland which suffered from the change seen in Basedow's disease.

Although Askanazy himself is of another opinion, I think this case supports the theory that the pineal body inhibits the premature development of the sexual organs in the female as well as in the male; and I believe firmly that the theory is valid, for my experimental results in the case of the female chicken prove it conclusively.

**Summary.** 1. Pinealectomized young cocks grow more rapidly than the controls, begin to crow prematurely, and show an earlier development of the combs and testes.

2. Pinealectomized young hens reveal likewise a premature development of the ovary and Fallopian tube.

3. In the pinealectomized chickens the endocrine organs, except

\* The report of this case will appear in the festival publication dedicated to Prof. S. Kure.

for the sexual glands, show nothing abnormal, or only a slight difference, as compared with those of the controls.

4. Therefore it appears that the pineal body's chief function is to repress the premature development of the sexual organs in the female as well as in the male.

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## THE RELATION OF ADDISON'S DISEASE TO AMYLOIDOSIS.

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IN spite of the differences of opinion that still prevail as to the essential pathological anatomy of Addison's disease, it is generally agreed that the vast majority of cases are associated with bilateral destructive changes in the adrenal glands. Most frequently, these lesions are tuberculous; next in order come atrophic changes often due to inflammation and hemorrhage; less commonly, bilateral tumors are found. Among the rarer conditions, gummata, thrombosis, and amyloid have been described.

Amyloid infiltration of the adrenals is a fairly common finding in individuals who have shown no evidence of Addison's disease. Such a condition is not infrequently met with in our autopsies in cases of widespread amyloidosis. The amyloid is present chiefly in the cortex, being deposited between the capillary walls and the parenchymatous cells. The latter undergo atrophy, presumably from pressure and from diminution of the blood supply. In the medulla, amyloid is present as a rule only in small amounts and about the bloodvessels.

But the association of amyloidosis and Addison's disease is an excessively rare one. Indeed only 2 cases have been found in the literature.<sup>1 2</sup> It should be instructive, therefore, to consider the relation of these two conditions.

The rarity with which amyloidosis produces Addison's disease may be due to the fact that the amyloid lies mostly in the cortex, while the medulla escapes. This explanation would be in harmony with the views of Wiesel, who believed that Addison's disease is always dependent upon lesions of the chromaffin system, whether within the medulla or elsewhere in the body.<sup>4</sup> Von Hanseemann<sup>4</sup> and Karakascheff,<sup>5</sup> however, reported cases of clinically typical Addison's disease in which the cortex was severely involved while the medulla remained intact. To this, Wiesel objected that these authors had not investigated the extra-adrenal chromaffin-tissue, changes which might have produced the symptoms. This objection is hard to dispose of conclusively, but it must be recalled that in the human adult the adrenals contain the bulk of the chromaffin-tissue; and if this be preserved, it is surprising that lesions of smaller chromaffin collections should suffice to determine the appearance of symptoms.

Recently, Fahr and Reiche<sup>6</sup> have reported 5 more cases of Addison's disease, with cortical lesions and preserved medulla.

They concur in what is perhaps the most satisfactory opinion, that destruction of either part of the glands is likely to be followed after a shorter or longer interval by the appearance of Addison's disease. It seems probable that products of protein splitting, possibly toxic, are taken up by the adrenal cortex and worked over there, and that from this material the medulla then forms adrenalin. Interruption of this process at either stage might, then, lead to adrenal insufficiency.

If, then, the cortical position of amyloid is inadequate to account for the non-appearance of Addison's disease, we must look for another explanation. This is probably to be found in the fact that in amyloidosis there does not occur complete destruction of the cortical cells, but merely an atrophy and loss of some of them. The remaining cells are presumably capable in most cases of carrying on their necessary function. But in the case herewith reported, either due to excessive injury of the cortex, or to other unrecognized factors, the function of the cortex would seem to have broken down, and the characteristic symptoms followed.

REPORT OF CASE.—*History*.—R. S., adult white female, aged fifty-three years, was admitted to the Philadelphia General Hospital complaining of weakness and swelling of legs and feet.

She stated that she had been well until one year before admission, when she noticed muscular weakness, with some loss of weight. This was followed by marked swelling of both upper and lower extremities. About four weeks before admission epileptiform convulsions began to occur, during which the patient was unconscious. There was occasional vomiting. About this time, she noticed that the color of her skin was altered.

The previous medical history was practically negative.

Physical examination showed a very ill woman with bronzed skin, and dark patches on the mucous membrane of the mouth. She was edematous over the entire body.

In the abdomen a mass was palpated in the region of the cecum. The reflexes were normal. The blood-pressure was 95 systolic, 45 diastolic. On two subsequent examinations the systolic pressure was 95, diastolic 55 and 50.

*Laboratory Examinations*. The urine showed a trace to a heavy cloud of albumin, a specific gravity of 1010 to 1018, a few hyaline casts, and variable numbers of leukocytes. Blood urea-nitrogen was 20 mg., uric acid 6.6 mg., chlorides 570 mg. Blood counts gave 3,960,000 and 3,270,000 red cells, hemoglobin 50 per cent, leukocytes 9450 and 6000, with 53 per cent polymorphonuclears. Blood and spinal fluid Wassermann were negative.

*Course*. During her stay of three months in the hospital, the patient had a number of epileptiform convulsions, which could be controlled fairly well by sedatives. She grew gradually weaker, became semistuporous during the last week, and died.

*Autopsy.* At autopsy the chief findings were as follows: There was a diffuse bronzing of the skin, most marked over the abdomen and breasts, where the pigmentation was nearly black. The lower pole of the right kidney was occupied by a yellow tumor mass, measuring 10 x 10 x 9 cm. No metastasis of the tumor was found (but the brain was not examined). The adrenals were of normal size and shape, but of increased consistency. The cortex was pale yellow to gray. The amyloid reaction with Lugol's solution was positive in the pulmonary artery, the walls of the cardiac chambers except the left ventricle, the aorta, spleen, liver, and left kidney. The adrenals gave a faintly positive reaction with the iodine solution.

Histological examination of both adrenals showed a deposition in the cortex of a glassy homogenous material, occurring in streaks, which lay in the transverse axis of the gland. This substance gave the color-reaction for amyloid with iodine, methyl-violet, and cresyl echt violet. It was so plentiful in the zona fascicularis and zona reticularis that the adrenal cells were present only here and there, scattered through the hyaline material. Nuclei were in some cases well preserved, in others, pyknotic. The cytoplasm was indistinct and the cell outline indefinite. Here and there could be seen the remains of columns of adrenal cells, which had the usual vacuolated appearance. The zona glomerulosa was much less involved than the deeper layers.

The medulla was scanty but well preserved, the cells staining normally. Amyloid was scanty, being chiefly confined to the walls of the bloodvessels, though extravascular collections of the material were seen in some places.

A small collection of ganglion-cells was found outside the adrenal substance. Many of the cells had poorly staining nuclei and some of the cell-bodies were ragged in outline.

Section of the kidney tumor showed a typical hypernephroma of the Grawitz type.

Although amyloidosis is usually the result of chronic suppurating conditions, yet it is not very infrequently found in individuals with malignant tumors, such as hypernephroma. That the tumor was responsible for the amyloidosis in this case cannot be doubted, since no tuberculous or suppurative lesions were found.

**Summary.** 1. A case of Addison's disease is reported, associated with widespread amyloidosis, which involved the cortex of both adrenals.

2. The amyloidosis apparently resulted from a large hypernephroma.

3. It is held likely that the rarity with which amyloid disease produces the Addison syndrome is not dependent on the preservation of the adrenal medulla, but rather on the fact that the cortex is not completely destroyed by the infiltration, many cell-groups escaping.

4. In the present instance, the destruction of cortex seems to have been severe enough to determine the appearance of Addison's disease.

The author is indebted to Dr. J. H. Musser, Jr., for the use of his clinical notes.

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### LYMPHATIC OBSTRUCTION: NON-PARASITIC ELEPHANTIASIS.

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UNDER the names of "chronic trophedema,"<sup>1</sup> "œdeme dystrophique,"<sup>2</sup> "elephantoid edema"<sup>3</sup> and "non-parasitic elephantiasis"<sup>4</sup> has been described an edema occurring in non-tropical climates which is characterized by a slow, insidious onset and a chronic, painless non-inflammatory course. The edema is commonly white and hard and free from tenderness on pressure. The lower extremities are most often involved and the subcutaneous tissues and to a lesser extent the skin are alone affected. Sensory changes are very rare. The general health is unimpaired, the common systemic diseases associated with edema are absent and the patient's chief complaint is of the weight or size or unsightliness of the parts in which the chronic enlargement exists.

Except for the lack of a hereditary or familial character, the diseases in this category present precisely the clinical picture described by Milroy,<sup>5</sup> Meige,<sup>1</sup> Rolleston<sup>7</sup> and Hope and French,<sup>8</sup> and variously interpreted as due to trophic changes or vascular neurosis.

In the past year we have had the opportunity of studying 5 cases of chronic edema of the sporadic type, all quite lacking in history of inflammation, particularly of erysipelas or other skin affections. All of these patients were women who gave, in every case, a history of very gradual onset and exhibited varying degrees of persistent swelling of a duration of from nine months to over thirty years.

CASE I.—G. C., aged twenty-two years, female, single, Jewish, a saleswoman, was admitted to the Cornell Clinic on November 3, 1921, with swelling of both legs of six years' duration.

Her family was free from similar disease. She was born in New York City, and in her first decade had had measles, pneumonia and whooping-cough. In 1917, an acutely inflamed appendix was removed at the New York Hospital. No note of increased size of the legs was made at that time. The patient began to menstruate at fifteen years and her periods have been normal. She has had chronic constipation since childhood.

At sixteen she first noticed swelling in both legs, and it occurred "all at once," from ankles to hips on both sides. There was no pain, no redness nor any other evidence of inflammation. She went to many physicians and received many diagnoses, but the enlargement slowly progressed. She has remained at work constantly.

Physical examination discloses a well-nourished girl, of good development and color. Her weight is 120 pounds. The upper extremities and the shoulder and pelvic girdles are normal in contour and without fat deposition. The heart and lungs are clear and all the findings are essentially normal, except for the lower extremities, which are twice the normal size and approximately equal. The skin remains fairly soft and is white. There is no pitting on pressure. The subcutaneous tissues are evidently thickened. There is no tenderness. The resistance suggests fatty overgrowth, but the remainder of the body is normal and there is no evidence of endocrine disturbance, particularly of myxedema or hypothyroidism. There is no enlargement of the inguinal nodes, and no evidence, in the form of thickening, of thrombosis of the femoral vein. The swelling does not involve the labia or abdominal wall.

The roentgen-ray plate showed bony and muscular outlines of normal size, while the subcutaneous tissues varied from 1 to  $1\frac{3}{4}$  inches in thickness. The sella was negative. In the endocrine clinic no evidence of incretory gland disturbance was found; a chronic pelvic inflammatory condition related to the appendix was considered as a possible factor, causing lymphatic blockage, and the diagnosis of elephantiasis was accepted. The young woman will not consider surgical treatment; recently she has expended a considerable sum on "electricity," without improvement.

CASE II.—A. M., aged fifty-two years, female, married, American, an office manager, came to the clinic on May 15, 1922, because "her limbs were badly swollen and were getting worse."

In her family there was no similar condition. Her past history was one of excellent health. At the age of fourteen years, following a fall, she had a swelling of the left knee, which was placed in



a cast for six months, without improvement. The swelling went on until the entire left leg was involved, first from knee to thigh and then from knee to ankle. The patient was not aware of inflammation at any time and the enlargement has been free from pain. The condition progressed, and at the age of twenty-five years, eleven years after the onset, she was told she had kidney trouble. In 1901, she went through six weeks of typhoid fever without complications. In 1908, at the age of thirty-six years, she first noticed a swelling of the right ankle, and this went on until the enlargement reached the knee, beyond which it has not advanced. The size of her legs is affected by posture; she keeps her feet elevated at night in order to be able to get her shoes on in the morning. The advent of short skirts has accentuated the patient's distress over her large extremities. Her weight has been stationary for five years.

The physical examination shows a well-developed and well-nourished, but not obese, woman of middle age, without abnormal findings except for the marked enlargement of the lower extremities, particularly from knees to ankles. The right calf at its mid-portion measures 19 inches and the left 22 inches in circumference. There is no pitting and no tenderness. The thighs are soft, perhaps slightly larger than normal. The skin over the legs is dry, firm, not to be picked up between the fingers, and very slightly reddened. There are no enlargements of the inguinal nodes. Pelvic examinations have been negative repeatedly and the Wassermann test is negative.

CASE III.—J. F., aged twenty-three years, female, single, stenographer, came to the clinic on June 15, 1922, because of swelling of the right leg of nine months' duration. She had been told she had phlebitis.

The family history is negative. The past history includes "St. Vitus' dance" for nine months at the age of fifteen years. She had no tonsillitis or rheumatic fever. Her cardio-respiratory and gastrointestinal history is entirely negative. Her menses began at fourteen years and she "grew up suddenly" in the year following. Her periods occur every twenty-eight days, last five days, with moderate flow and without pain. She was born and has always lived in New Jersey, and her habits are unexceptionable.

The present illness began in September, 1921, when the patient noticed a swelling of the right ankle which was not associated with trauma or pain. The swelling progressed slowly and painlessly, and three months later there was a noticeable enlargement from the ankle to the hip. The patient believes her leg is still getting larger. It varies with posture, decreasing with elevation. At no time has there been tenderness, and no inflammation of the skin has been present. The girl complains of some stiffness in the

right hip. She has gained weight. At the time of the onset of the swelling in the ankle she thinks the right labium was slightly swollen.

The examination discloses a moderately tall and slender girl, of fair development. Her weight is 111 pounds. Her color is good, the pupillary reactions are normal, the tonsils are small, the teeth are excellent and the thyroid is not felt. The heart, lungs and abdomen are without pathological findings. The right leg is swollen from the hip down. There is pitting on pressure over the right tibia. The skin remains soft and is not discolored. There are no varicosities. The inguinal nodes are not enlarged. The deep vessels in the groin are not palpably thickened. The left leg is normal. The comparative measurements are: Mid-thigh: right, 18 inches; left, 15½ inches. Mid-calf: right, 14 inches; left, 12 inches. The knee-jerks are normal. The blood-pressure is 108 systolic and 72 diastolic. There is a very faint trace of albumin in the urine.

The diagnosis of lymphatic blockage was proposed and the question of curative treatment discussed. The patient has never returned for the surgical consultation, as she was directed by friends to a doctor who had just returned from a trip to the Orient and knew that her condition could not be elephantiasis. She has written that she is being treated for a thrombosed vein with elevation of the foot and tablets to "dissolve clot." A recent letter states that she feels better, but the swelling is still present.

CASE IV.—R. H., aged fifty-eight years, female, married, German, housewife, was admitted on July 20, 1922, with the complaint of swelling of the legs and backache.

Of the family history, the patient remembered that a sister in Europe had a swelling of the legs but was ignorant of its nature. Her past history was one of robust health. She had born 11 children without miscarriage, "milk-leg" or other complications. The pain in the back was of some years' standing.

The present illness dated from 1920, when swelling of both legs became rather marked. By the time of her second visit, however, she had remembered that she had noticed slight swelling, beginning twenty years previously, at the age of thirty-eight years. She had been treated in Bucharest and other Continental clinics without improvement. She had had no pain or inflammation, and she came to get medical attention only when a friend commented upon the size of her swollen feet.

This patient is an obese woman, weighing 167 pounds. The physical examination is essentially negative. There is no definite localization of the fat and no evidence of endocrinopathy. The thighs give normal measurements, 21 inches in their midportion on each side. From the knees to the ankles there is marked enlarge-

ment of both legs, measuring  $15\frac{1}{4}$  inches at the midpoint of each calf. There is no pitting, no tenderness and little pigmentation. The subcutaneous tissues are thickened. There are slight superficial venous varicosities. No enlargement of the lymph nodes were made out in popliteal or inguinal regions.

The urine and blood-pressure are normal.

CASE V.—N. W., aged twenty-eight years, female, single, Irish, telephone operator, came to the clinic on February 16, 1922, for a cold in the head. This was relieved and the patient was not seen until October 30, 1922, when she returned for indigestion, and was sent to the department of medicine for the first time. Her family history was negative. Her past history was free from illness, except for influenza in 1919. Her present illness, "heavy stomach," gas and occasional "cramps," is of a year's duration. She is afraid of cancer. Her physical examination is entirely negative, except for marked enlargement of the legs below the knees. Questions regarding this bring out the facts that the swelling began at the age of fourteen years with the establishment of menstruation. There was slight tenderness of the skin at the beginning, but no inflammation and no fever. The size of the lower legs has always annoyed her and for the past two years has been increasing slightly. The legs are definitely larger at night than in the morning. At the present time the skin is slightly thickened, the subcutaneous tissues more so. There is no pitting at this examination and no tenderness. The blood-pressure is 104 systolic and 62 diastolic. The urine is normal.

The question at once arises whether such conditions as are presented in these patients may be grouped correctly under the heading of elephantiasis, a term which, of course, serves to call to mind the huge pachydermous enlargements associated with filariasis and lymphatic obstruction which give the tropical disease its name. The characteristic features of elephantiasis, strictly speaking, are two in number: Chronic edema and proliferation of the subcutaneous connective tissue secondary to this edema, and the pathological basis for the edema is the blocking of the lymph circulation.

Manson<sup>9</sup> states that "lymph stasis alone does not produce elephantiasis," by which he means a true hypertrophy of the subcutaneous tissue, for which "inflammation in an area of lymphatic congestion is prerequisite." He further states that "simple lymphatic edema in areas which have never become inflamed subsides readily enough on pressure or elevation."

Matas<sup>3</sup> defines elephantiasis at some length as "a progressive histopathological state or condition which is characterized by a chronic inflammatory fibrosis or hypertrophy of the hypodermal

and dermal connective tissue, which is preceded by and associated with lymphatic and venous stasis, and may be caused by any obstruction or mechanical interference with the return flow of the lymphatic and venous currents in the affected parts." Matas also maintains that mechanical obstruction alone is not sufficient to cause this characteristic hypertrophy of the subcutaneous tissues, but that secondary and repeated bacterial invasion, usually streptococcal, is essential. Such secondary infection, he states, is required whether the primary obstruction is due to filariæ, to lymphangitis, to adenitis or to thrombophlebitis; and the tropical incidence of the disease is due not to filariasis chiefly, but to the greater exposure of the unclothed body to traumata, parasites and infections of the skin.

That lymphatic obstruction alone may be the cause of persistent edema that is little or not at all relieved by such measures as elevation, compression and massage is shown by the disappearance of the edema when new channels are provided for lymph flow. Indeed, a brilliant chapter in the physiology of the lymph circulation has been contributed by recent surgery, and it is the possibility of great and permanent relief by an operative procedure attended by very little danger that makes the recognition of this disorder of importance.

In the study of edema of the arm associated with the more chronic forms of mammary carcinoma, either with metastases to the axillary nodes or their excision, Handley<sup>10</sup> was able to exclude venous obstruction as a factor by reason of the absence of edema after excision of the axillary vein or its total compression by cancerous masses. By the use of silkworm gut as a means of replacing the occluded or absent superficial lymphatic channels, he met with notable success in reducing the edema. The same was not true when he and others attempted this means of drainage in the leg. But this work goes to show clearly enough that lymphatic blockage alone causes persistent edema and that the definition of elephantiasis will gain in clearness if venous obstruction as a cause is excluded.

The treatment of chronic edema in the lower extremity was solved by Lanz<sup>11</sup> in a case of elephantiasis of five years' duration. The onset had been slow and painless until the size and weight interfered with the man's work. Elevation of the leg brought no result. Multiple incisions of the fascia lata and fascial strips into the marrow of the femur resulted in permanent relief of the edema. The operation served to confirm the anatomical observations of Sappey<sup>12</sup> and the later studies of Delamère, Poirier and Cuneo,<sup>13</sup> which showed the independence of the superficial and deep lymphatics of the extremities, the deep fascia forming an absolute barrier in contrast with views fairly commonly held of the free anastomosis of the lymphatic vessels. As another means

of replacing lymph channels, Lanz suggested transplantation of the spermatic cord, with its rich lymphatics, to bridge an inguinal barrier. Although this was never knowingly carried out, it is of interest that one of Milroy's series, a male born with edema of the foot, had testicular enlargement at maturity, and an operation for removal of the testicle was followed by permanent disappearance of the edema.

Kondoleon<sup>14</sup> followed with a simplified technic of fascial division and removal and reported a series of successes that have attracted general attention. From his large experience, Kondoleon divides elephantiasis into a milder form manifesting only lymph stasis and the more advanced sclerotic type—the result of connective-tissue proliferation. The causes of lymphatic obstruction in his cases included acute inflammations of the foot, tuberculosis of the knee-joint, total extirpation of the inguinal nodes and traumata. There was absence of any injury or inflammation in the case of a woman, aged thirty years, with involvement of the entire right leg for ten years. The formation of new lymph channels after operation was indicated in a patient with edema of fourteen years' duration by the recurrence of the edema shortly after operation and its subsequent spontaneous subsidence. Kondoleon found the lymph stasis occurring chiefly at the fascia lata in his cases; the superficial layers of the fascia were thickened while the surface toward the muscle was always normal. The skin in these patients varied, but was in general moderately thickened, pale, hard and not to be picked up in folds. In one patient there was free exudation of a serous yellow fluid.

Summarizing these cases that have come to operation and others reported by Matas,<sup>3</sup> Sistrunk<sup>15</sup> and other surgeons in this country, conclusive evidence is presented of the role of lymphatic blockage in the production of persistent edema and subcutaneous thickening such as form the chief characteristics of the cases in our series. Following the grouping adopted by Bradbury,<sup>4</sup> the cases that fail to give a history or signs of inflammation may be satisfactorily classified as non-parasitic elephantiasis in contrast with elephantiasis arabum of filarial origin and elephantiasis nostras following erysipelas or frank bacterial infection. When the dystrophic edemas and trophedemas of the French and English writers are considered in the light of the newer lymphatic knowledge, one is inclined, in the absence of definite neurological findings, to include these forms, as well as various isolated cases of unsatisfactorily explained chronic edema (myxedema fruste, Hertoghe, and segmentary edema, Debove) under the heading elephantiasis.

The differential diagnosis of elephantiasis, or edema due to lymphatic obstruction, is of considerable interest. All of the many causes of edema are to be passed in review, and most of them, such as cardiac decompensation, renal disease, the blood

dyscrasias and nutritional disturbances can be promptly excluded. The edema that follows phlebitis is rarely of such long standing, or so firm in consistency, and here also there is rarely lacking a definite history of localized inflammation usually occurring after some primary disease. The question of obesity, either general and due ordinarily to sedentary life, and too much food, or localized and due to endocrine disturbances, notably hypothyroidism and hypopituitarism,<sup>16 17</sup> must be considered; but this can usually be decided from the history and the physical characteristics of the enlargement. Myxedema also is differentiated by its characteristic signs and history. The acute swellings, of the nature of angioneurotic edema, do not, of course, enter into consideration. There is a small group of edemas associated with disease of the central nervous system, with or without muscular paralyses, and probably due to vasomotor changes, as in the classical Ranvier section of the sciatic nerve after the femoral vein had been ligated. In another small group, called by Krehl<sup>18</sup> "essential" edema, no explanation in the way of an external factor causing edema could be found.

In the cases of this series the edema might be regarded as "essential" were it not for what has been definitely shown of lymphatic obstruction and its relief. One can only speculate why all of these cases occurred in women, and in 3 of them at the age of puberty. One of Sistrunk's cases was a girl of seventeen years, whose right leg began to swell at the age of twelve without apparent cause, though she had infected tonsils. Benedict's<sup>6</sup> two cases were women of middle age, with onset of unknown origin. Only one man in this clinic has been seen with edema of more than a few weeks' duration, and that in a patient with recent pneumonia and typical femoral phlebitis. In these women, then, in the absence of anatomical evidence of obstruction such as enlarged nodes or lymphangiectases and clinical manifestations, past or present, of infection, one must be content with suggesting chronic lymphadenitis, chronic lymphangitis, traumata and compression as the result of circulatory or inflammatory changes within the pelvis as etiological possibilities.

The physiology of edema has been adequately discussed by numerous writers,<sup>19 20</sup> and the basic fact is that when lymph production exceeds lymph absorption edema results. The production of lymph under the wide range of pathological conditions associated with edema has given rise to an equal diversity of theories recording its formation. During life only the great lymphatic trunks can be distinguished, and the study of the system post mortem has great technical difficulties. Consequently, the obscurity in which the lymphatics have remained in contrast with the other two great divisions of the circulatory system. It is necessary to remember, as Sabin<sup>21</sup> has pointed out from her beautiful embryological studies, that the lymphatic problem is a fundamental part of the vascular problem.

**Summary.** Five cases of persistent edema associated with thickening of the subcutaneous tissues and minor skin changes are reported. The edema is hard, white and not accompanied by sensory changes. The absence of frank inflammation at the onset or during the course of the disease is striking. The general similarity of these cases to what has been described as trophedema and dystrophic edema is pointed out. Except for the lack of a hereditary or familial character this type of edema bears a remarkable resemblance to the disease first described by Milroy.

Edema as found in these patients, in the light of recent knowledge, appears to be due to obstruction of the lymphatic channels and may be classified as elephantiasis of a non-parasitic type. Surgical treatment of these cases alone gives a good prognosis as regards their cure.

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#### AN ANATOMICAL BASIS FOR FUNCTIONAL MURMURS.

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THE interpretation of cardiac murmurs has always been of great interest and uncertainty. Errors in the diagnosis of murmurs are not infrequent and their clinical deductions are not always borne out by the pathological findings. All murmurs indicate

some abnormality in the cardiovascular structure. A murmur is an echo of a vibrating heart or bloodvessel, caused by the blood stream being compelled to detour its course, traverse a rough surface, or strike against an inefficient or relaxed valve. While a murmur does not always mean a sick heart and the absence of a murmur does not prove a sound heart, yet a murmuring heart shows that there is something out of order. A murmur may be consistent with perfect health, or it may presage a gradual cardiac decadence.

In the routine examination of patients one frequently finds a cardiac murmur without any other evidence of heart disease to which the name of accidental, inorganic, hemic, or functional murmur has been applied. Accidental murmur is a meaningless term and should be discarded. Inorganic murmur is an ill-adapted term, as all changes in the heart are of a living character. Hemic murmur suggests that the murmur is caused by anemia. But not all anemic patients have murmurs. I have examined a number of anemic patients with a view to finding a cardiac murmur and have found a hemic murmur in a limited number of cases only and without any definite relation to the severity of the anemia. The anemia is probably a contributing factor and the real cause for the murmur may be found in some anomaly of the cardiac muscle tissue. Functional murmur has no generic significance unless it implies a definite cardiac function which, when disturbed, gives rise to a murmur. It is only when a murmur is caused by some abnormality in one of the physiological cardiac functions that the term functional murmur becomes intelligible.

Functional disorders whether applied to cardiology, neurology, or to any other branch of medicine lacks clearness of meaning. As there is no living structure without function so there is no function without structure and disturbances of function must necessarily imply disturbances of structure whether they are perceptible or not. And functional murmurs must therefore have an anatomical substratum.

The heart in its normal action is governed by the following five physiological functions: Stimulus production, excitability, conductivity, contractility, and tonicity. In concord with the skeletal muscle, the cardiac muscle is always in a state of tonus. The heart never relaxes entirely during its restful period or diastole. It always maintains a certain amount of tonic contraction.

Any local or general disorder which will lower the physiological function of tonicity will give rise to a condition of atonia cordis or myatonia cordis. The heart is then unable to contract forcibly during systole and is unduly relaxed and dilated during diastole. There may be a certain amount of residual blood in the ventricles after cardiac contraction. With each impact of blood during systole the relaxed heart and its valves vibrate and there may be



a slight regurgitation. This cardiac vibration gives rise to a soft blowing systolic murmur which has received a variety of names. But since the murmur is the result of some alteration in a physiological cardiac function, namely, tonicity, the term functional murmur has the nearest claim.

Whether the so-called functional murmur with its possible slight regurgitation serves some useful purpose in the mechanism of the heart and in that sense it is purely physiological, or it borders on the realm of the pathological, is still a mooted point. Patients are frequently seen who for many years have this blowing systolic murmur with no apparent impairment of health. In others with the same kind of murmur there is evidence of a general muscular weakness, the blood-pressure is low, and there is a drooping of the heart and abdominal organs.

In all cases of functional murmurs there is evidently no anatomical damage or circulatory inefficiency, but a condition of a lower grade of cardiac tonus. This may be a congenital peculiarity of the cardiac musculature, as the soft blowing systolic murmur is quite frequently heard in infants and young children and persists to adult life. The presence of this murmur in early life and its persistence for many years suggests a congenital origin. The acquired functional murmurs which are heard in older children and adults may be caused by febrile conditions, cardiac fatigue, anemia, malnutrition, improper cardiac innervation, and by hypoadrenia, when acting on a heart of poor muscular tonicity. This murmur usually disappears with the removal of the cause which lowered the muscle strength.

The murmur may be heard in any of the valvular regions but especially in the mitral and pulmonic areas. The diagnosis of a functional murmur is occasionally difficult. Endocardial and myocardial murmurs, during good compensation, and certain cardiopulmonary murmurs, may at times, be indistinguishable from functional murmurs. But if to the objective sign of a soft blowing systolic murmur, limited in its extent, in a heart of normal dimensions, there will be added the health of the patient and his previous history, the diagnosis will become comparatively easy. It is the patient behind the murmur that makes the diagnosis in doubtful cases.

As tonicity is one of the primary physiological functions of all muscle tissue and is an inherent quality of cardiac muscle, a myogenic property, a lowering of muscle tone must effect the final anatomical unit, the muscle fiber. Since the indefinite group of murmurs which are known as accidental, inorganic, hemic, or functional may be caused by a lack of cardiac tonus, the term myatonic murmur, to take the place of the miscellaneous names, would perhaps be more appropriate. It would at once suggest a physiological dysfunction and an anatomical basis.

**Summary.** In brief, a murmur is frequently heard in children and young adults which cannot be traced to embryological cardiac malformation, endocardial valvular deformity, or to myocardial disease. Because of its uncertain etiology it has received many names which are used carelessly and interchangeably. The uncertainty in the origin of this murmur has also led to its being either totally disregarded or too seriously evaluated. It is therefore of considerable importance for theoretical as well as for practical reasons to put this murmur on a certain scientific basis.

Since nothing constant or definite has been found in the heart or in its circulating fluid to account for this murmur, it is evidently not caused by pathological changes in the cardiac structure, but by physiological disorders in some function of the cardiac muscle tissue; that is, by physiological dysfunction in the cardiac anatomy. Atonia cordis, or a deficiency in the physiological function of cardiac tonus may be the basis for this murmur. Cardiac hypotonia may be of congenital origin or caused by malnutrition, anemia, cardiac fatigue, hypoadrenia, improper nerve control, or by febrile diseases. An atonic, relaxed heart will be unduly stretched by the sudden intraventricular impact during systole and give rise to abnormal vibratory movements and to a soft systolic murmur. The murmur will appear or disappear with the underlying condition that lowered the cardiac muscle strength. This is probably the origin of the oft-heard systolic murmur on which was bestowed a variety of names. But since the origin may be traced to a defective cardiomuscular tonicity, the condition may properly be called myatonia cordis, and the murmur itself myatonic murmur. The diagnosis rests on the fact that the murmur is an isolated objective sign without subjective symptoms and without a history of a previous heart-damaging illness. The prognosis is generally good, but there is always an element of uncertainty, because a perfectly normal heart does not murmur. The treatment is that of the patient and not of the heart.

## PAROXYSMAL VENTRICULAR TACHYCARDIA:

### Report of a Case of Unusual Type.

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PAROXYSMAL tachycardia of ventricular origin is sufficiently uncommon to warrant the reporting of isolated cases. It can only be definitely differentiated from that of auricular origin by means of the electrocardiograph. It is the result of a rapid and regular succession of ventricular ectopic beats.

The relative frequency of its occurrence may be judged by the following statistics. Among 2400 soldiers invalided during the recent war for D.A.H. and V.D.H., Hume found 6 cases of paroxysmal tachycardia, which he described as of ventricular origin. In 3 of these cases electrocardiograms were obtained, 2 of which were undoubtedly cases of this condition. Willius gives the occurrence as .04 per cent of all abnormal electrocardiograms encountered at the Mayo Clinic. Hart records 1 case in a series of 17 cases of paroxysmal tachycardias, while Vaughan found 2 among 18.

The incidence of this type of arrhythmia is definitely less frequent than the foregoing statistics would indicate. In a recent review of this subject made by Robinson and Hermann of all the cases of paroxysmal tachycardia of ventricular origin which were previously published with electrocardiograms they have come to a similar conclusion. Of 16 cases so recorded only 6 were acceptable by them as undoubted cases of paroxysmal tachycardia of ventricular origin; while 6 other cases were considered as probable.

This is explained by the fact that isolated auricular extrasystoles may at times be followed by varying degrees of blocking in the ventricular conduction system, as originally pointed out by Hewlet. Furthermore, electrocardiographic studies have shown that this disturbance may be limited to either branch of His's bundle and will be recognized as aberration of the ventricular complexes. In high grade tachycardia the conduction through the ventricles is more likely to become defective and aberrations of the ventricular complexes appear in the electrocardiograms. In a prolonged paroxysm it is manifestly impossible, because the aberrations resemble closely ventricular extrasystoles, to distinguish an auricular from a ventricular paroxysm of tachycardia, unless distinct evidences of the auricular activity are visible at a slower and independent rate. The most certain way of unravelling the tachycardia is by careful analysis of the onset or offset of an attack, especially the type of extrasystoles occurring during these transitional stages. If these are typically ventricular in form and identical with those occurring during the spell, we can be reasonably certain that the site of impulse formation during the abnormal rhythm is in the ventricles. Unfortunately it is not always possible to record these transitions and many cases must be left in doubt. In cases of established auricular fibrillation such difficulties as a rule do not arise, the tachycardia, if paroxysmal is unquestionably ventricular in origin.

The following tabulation shows at a glance the essential clinical and pathological data of all the cases reported in the literature with graphic records.\*

\* Since this article was accepted for publication another case appeared in the literature. This was an undoubted case of ventricular tachycardia, the site of origin of the abnormal rhythm was in the right ventricle, and caused retrograde contraction of the auricles. The attacks were successfully controlled by quinidine.

EDITORS' NOTE.—Four cases have recently been reported by C. C. Wolferth and T. M. McMillan (*Arch. Int. Med.*, 1923, 31, 184) and one by Gallivardin (*Arch. d. mal. du cœur*, 1922, 15, 298.)

Authors.	Undoubted cases.		Probable cases.		Doubtful cases.		Site of ectopic foci.	Autopsy findings.	Remarks
	Sex.	Age.	Sex.	Age.	Sex.	Age.			
Lewis	M.	..	..	..	..	..	Right ventricle	.....	Independent auricular activity visible.
Hart	M.	49	..	..	..	..	Left ventricle	.....	Independent auricular activity visible, probably retrograded from ventricular. Syphilis? Improved.
Cohn and Fraser	..	..	M.	43	..	..	Right ventricle	.....	Left vagus pressure controlled attack.
Butterfield and Hunt	M.	45	..	..	..	..	Left ventricle	Sclerosis of mitral and aortic valves. Extensive degeneration and fibrosis of left ventricle and septum	
Willius	M.	62	..	..	F.	21	Right ventricle	In one case autopsy showed atheroma of left coronary artery	Probably auricular tachycardia.
Vaughan	M.	42	..	..	..	..	Right ventricle	.....	C. C. V. D. mitral and aortic insuff. hypertrophy. Auricular tachycardia followed by ventricular tachycardia.
	..	..	F.	44	..	..	Left ventricle?	.....	
Hume	M.	21	..	..	..	..	Left ventricle	.....	Probably auricular tachycardia.
	M.	50	..	..	..	..	Left ventricle	.....	
Lea	M.	..	..	..	M.	20	Right ventricle	.....	All in soldiers with no evidences of cardiac disease.
	M.	..	..	..	..	..	Left ventricle	.....	
Gallavardin	M.	59	..	..	..	..	Left ventricle	Aorta and coronaries markedly atheromatous	Auricular fibrillation with high degree of A-V block. Attack of ventricular tachycardia studied by polygraph record.
	..	..	M.	63	..	..	Left ventricle	Extensive atheroma of aorta. Valvular and myocardial sclerosis	
Robinson and Herrmann	M.	59	..	..	..	..	Left ventricle	Syphilitic aortitis and coronary plaques in left ventricle	Auricular activity visible. Controlled by vagus pressure.
	M.	53	..	..	..	..	Left ventricle	Syphilitic occlusion of ant. descending branch of left coronary	
Schwensen	M.	58	..	..	..	..	Left ventricle	.....	Auricular fibrillation.
	F.	49	..	..	..	..	Right ventricle	.....	
Writer's case	F.	61	..	..	..	..	Rt. and lf. alt.	Old endocard. of mitral valve. Hypertrophy and dilatation	Auricular complexes? Chronic nephritis, exitus. Dropped dead six months after discharge. Lues, improved under treatment; auricular complex visible.
	F.	54	..	..	..	..	Rt. and lf. alt.	.....	
Total	18	..	5	..	2	..	Left ventricle 11		Chronic nephritis, arteriosclerosis, myocarditis, auricular fibrillation.
	M-15	..	M-4	..	M-1	..	Right ventricle 7		
	F-3	..	F-1	..	F-1	..	Left doubtful 2		
		..		..		..	Bilateral 2		

The condition is very much more frequent in males, and in all the cases except those reported by Hume, the patients presented evident symptoms of grave cardiac involvement. The death-rate has been extremely high. The frequent occurrence of coronary disease in this condition is to be noted, and is significant in view of the experimental production in animals of ventricular tachycardia by ligation of the coronary arteries. Syphilis has been a factor in a few cases. The possibility of digitalis producing paroxysmal tachycardia is discussed by Hart, Vaughan and Schwensen. It is known that experimentally paroxysms of ventricular tachycardia can be produced by chloroform, digitalis and strophanthin. In hearts that are badly decompensated, showing high degree of myocardial degeneration with extreme dilatation and in which digitalis medication is pushed, toxic effects are easily induced, such as coupling and even ventricular tachycardia (D. Danielpolu).

In all the cases so far published with electrocardiograms, the paroxysm was produced in a single focus arising in either ventricle, most frequently the left. The case which we observed at the Montefiore Hospital was unique and only recently Schwensen reported a similar case. In both the paroxysms were the results of alternately recurring right and left ventricular extrasystoles.

**CASE REPORT.**—H. G., female, aged fifty-four years, housewife, was admitted to the Montefiore Hospital December 30, 1920, complaining of the typical train of symptoms due to cardiac decompensation; namely general weakness, attacks of palpitation, dyspnea, orthopnea, swelling of the feet, ascitis, insomnia and frequency of urination. The family history was essentially negative.

*Past History.* She had had no serious illness until the onset of the present trouble. Menses appeared at twelve years, menopause at fifty years. She was married at twenty years, had 10 pregnancies, with 7 living children. She had 1 miscarriage,  $2\frac{1}{2}$  months, 10 years previously. Deliveries and puerperia were normal. There was no venereal history. She had always worked hard, had insufficient sleep and kept irregular hours. Was moderate in all other respects.

*Present Illness.* About six years previous to admission, after a hard day's work, patient had a sudden attack of faintness. Following this she was bedridden for six weeks. She had great difficulty in using her left arm and leg. The left eye remained open and her mouth was drawn toward the left. She had difficulty in speaking and chewing. At the end of about six weeks the symptoms cleared up. The following year the patient was able to go about her usual duties although she did not feel as strong as formerly. Three years ago she had a sudden attack of dyspnea, with cough and weakness, but no edema. A few weeks of rest cleared up the symptoms, the patient again resumed her work and since then

has had several similar attacks, feeling always weaker after each one. In August, 1920, she had a final attack and this time the dyspnea, cough and weakness were accompanied by palpitation, edema and ascites. A few weeks in one of the hospitals of the city resulted in the clearing up of the symptoms, except the weakness and shortness of breath. Two weeks before her entrance into Montefiore Hospital, the ascites returned and she was barely able to be up and about.

*Physical Examination.* The patient appeared much older than her age of fifty-four years. She was of medium stature, poor nutrition and the mucous membranes were slightly cyanotic. The nose and throat were essentially negative but all the teeth were missing. The pupils were slightly irregular, the right one being smaller and reacted sluggishly to light. There was a fulness and pulsation in the vessels of the neck, both venous and arterial.

The *thorax* was symmetrical and of fair size. The lungs revealed some dulness at both bases, where there were a few moist rales. The cardiac impulse was poorly discernible, diffused and the maximum impulse was felt in the sixth space in the anterior axillary line. No thrills were palpable. The transverse diameters were much enlarged. The heart was fibrillating, rapid and a systolic murmur was audible, best heard over the apex and transmitted into the axilla. The pulse deficit varied between 10 and 20 beats. The radials were thickened and the blood-pressure was 175/75.

The *abdomen* was pendulous; diastasis of the recti was marked. The dependent portions were edematous. The liver's sharp edge was palpable about four fingers below the costal margin, not pulsating but tender. The spleen and kidney were not felt and there was no ascites. There was slight edema of the lower limbs, and cyanosis of the nail beds. Neurological examination was essentially negative.

The urine was acid, the specific gravity varied from 1010 to 1025. There was always a trace of albumen but no sugar. During the last week blood cells were present, hyalin and a few granular casts were constantly seen.

The Wassermann reaction was negative.

The diagnosis was arteriosclerosis, chronic nephritis, endomyocardial disease with mitral insufficiency, auricular fibrillation and hypertension. Terminal paroxysmal ventricular tachycardia.

The first electrocardiograms were taken on January 7, 1921, and showed a typical auricular fibrillation of a fine character, with a left ventricular predominance. The rate of the heart varied between 94 and 150. The rhythm was completely irregular, but no premature beats occurred at this time. Fig. 1.

*Course.* During the first two months of her stay in the hospital, the patient improved considerably under medication with digitalis and theobromin sodium salicylate. The heart-rate became slower

and the dyspnea and other subjective symptoms diminished in severity. During the month of February, she developed an acute psychosis, lasting about two weeks and characterized by sleeplessness, irritability, disorientation and noisy delirium. With this her compensation suffered greatly, the pulse deficit increased and the edema of the limbs reappeared. There was an accumulation of fluid in the left pleural cavity, but not sufficient for aspiration. Her mental condition gradually cleared up, following which heavy

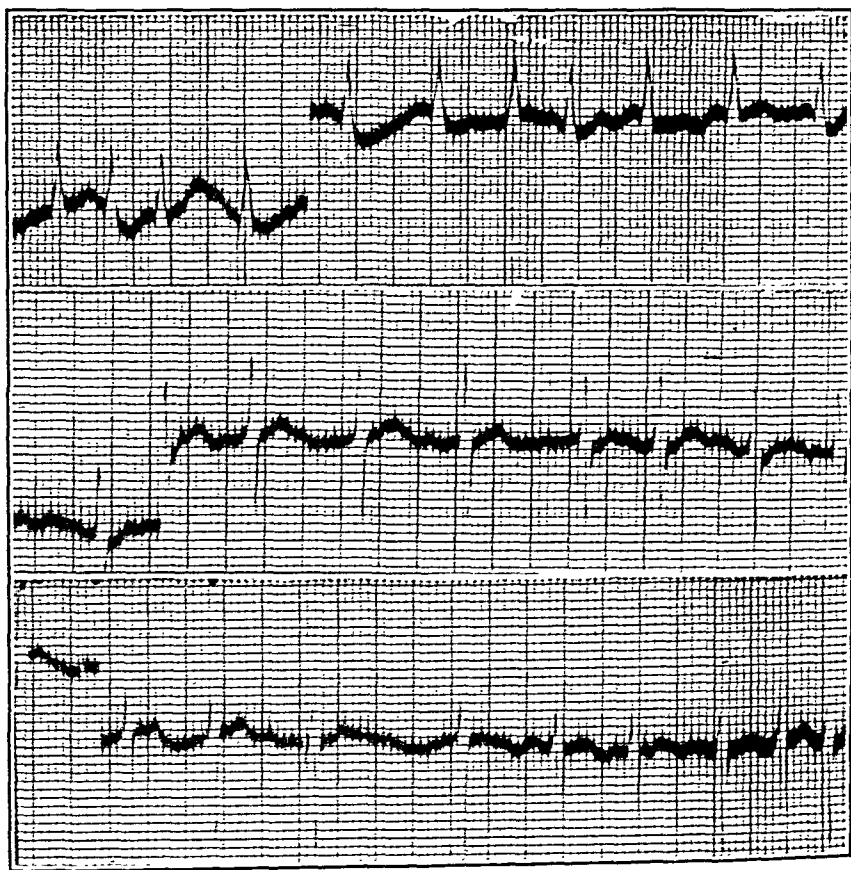


FIG. 1.—Record obtained January 7, 1921. Auricular fibrillation. Left ventricular preponderance.

doses of digitalis, theobromin sodium salicylate and a Carrel diet were instituted for the progressive edema. In spite of this the pulse remained rapid, irregular and a large pulse deficit was constant. The urine became very scanty and almost a complete anuria set in.

*The Paroxysms.* On March 18, 1921, the first attack of paroxysmal tachycardia occurred. The patient complained of abdominal pain, the pulse-rate suddenly rose to 150 per minute, and curiously

became absolutely regular. On the following day she vomited, the heart remained at 150 at the apex and it was noted that all the beats came through at the radials. These regularities of the pulse continued for varying periods during the day and would come and go suddenly. During the next few days the patient continued having tachycardia at irregular periods. By now the edema had increased decidedly, the orthopnea was very distressing, she was very uncomfortable and markedly cyanotic. Up to this time digitalis had been continuously administered in the form of tincture of digitalis, 30 minims thrice daily. This was begun on December 30, and discontinued March 20, 1921. The following day tachycardia had ceased, the pulse was 88 at the apex and 66 at the wrist. It was extremely irregular and numerous extrasystoles were made out. On March 22, the paroxysms returned, but at very irregular intervals. These periods continued until April 9, from which date the tachycardia became constant, the rate varied from 140 to 180 per minute, the pulse remaining constantly regular. The condition of the patient progressively grew worse, the apex of the heart passed out into the posterior axillary line and the liver rapidly enlarged and pulsated. Emaciation became extreme and she died on April 12, 1921. Autopsy was not obtainable.

**ELECTROCARDIOGRAPHIC FINDINGS AND DISCUSSION.** The second series of records (Fig. 2) were made on March 20, 1921, two days after the onset of paroxysms. These showed a very striking and unusual picture, which is best revealed in the third lead. The tachycardia was of sudden onset and was preceded by anomalous deflections identical with those of the paroxysms, and had the appearance of typical ventricular extrasystoles. They arise from both ventricles, and during the paroxysm these anomalous deflections succeed each other alternately in a regular fashion and apparently the stimuli producing the arrhythmia travelled to each ventricle alternately with perfect sequence.

Another series (Fig. 3) of electrocardiograms were obtained on March 23, 1921. The paroxysms were short and came on at irregular periods. The rhythm was extremely irregular between the attacks. This irregularity was the result of groups of extrasystoles forming bigemini or trigemini, and arising from multiple foci. In the third derivation we were fortunate in obtaining a paroxysm. The type of deflections were reproduced with most characteristic exactness, and the picture was identical with that obtained on March 20. During the irregular periods the coupling seen was very much like that of digitalis intoxication, and it is very suggestive that perhaps digitalis was the precipitating factor in inducing the paroxysm in our case. Recently, in experiments on cats with intramuscular injections of strophanthin, electrocardiograms were obtained in which a ventricular tachycardia was



induced, and the deflections alternated in a similar fashion, as seen in this patient. (Fig. 4.) Schwensen mentions that Lewis and

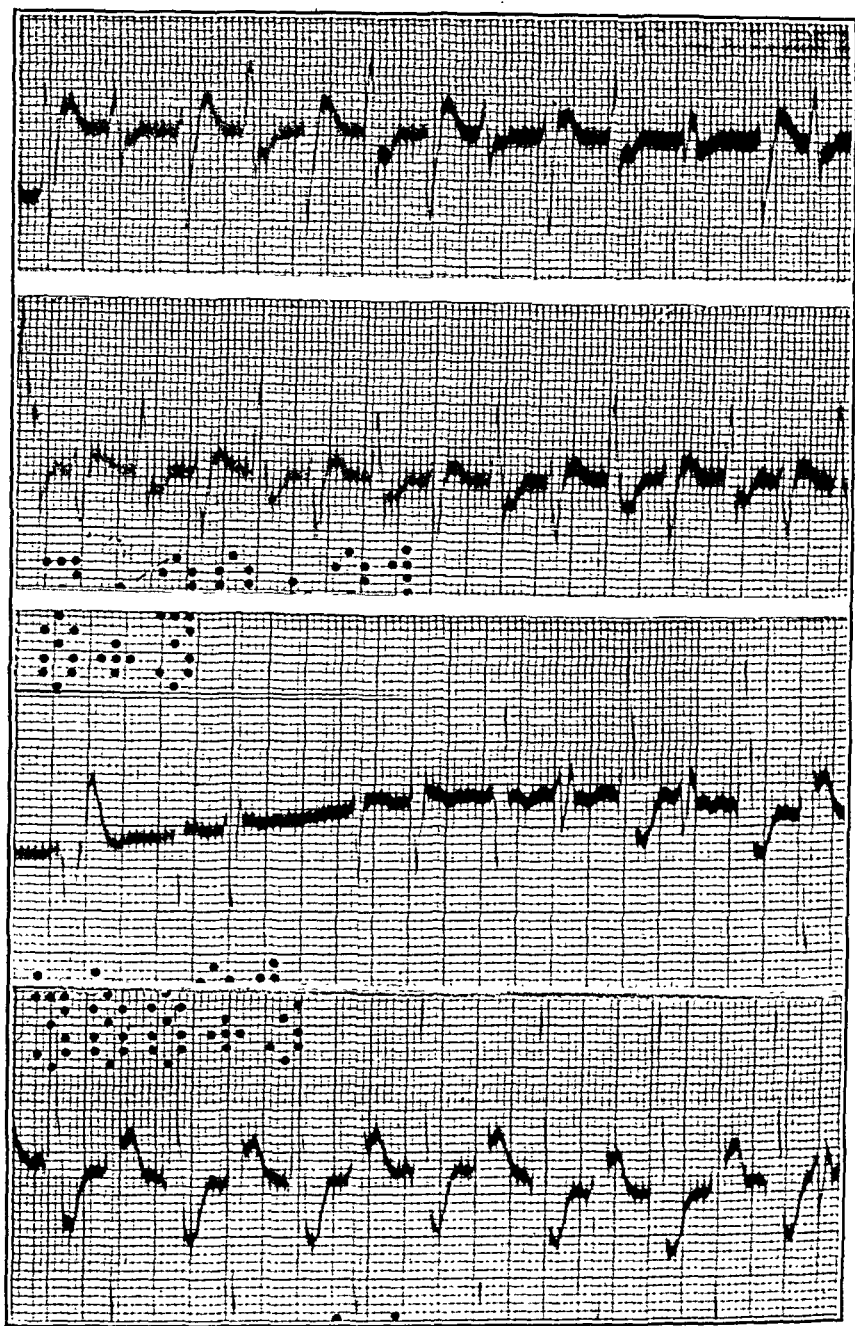


FIG. 2.—Paroxysm recorded March 20, 1921. Leads 1, 2 and 3. In Lead 3 (the last 2 records) the onset of a paroxysm is shown, preceded by premature beats similar to those seen in the continued paroxysm as depicted in the last record.

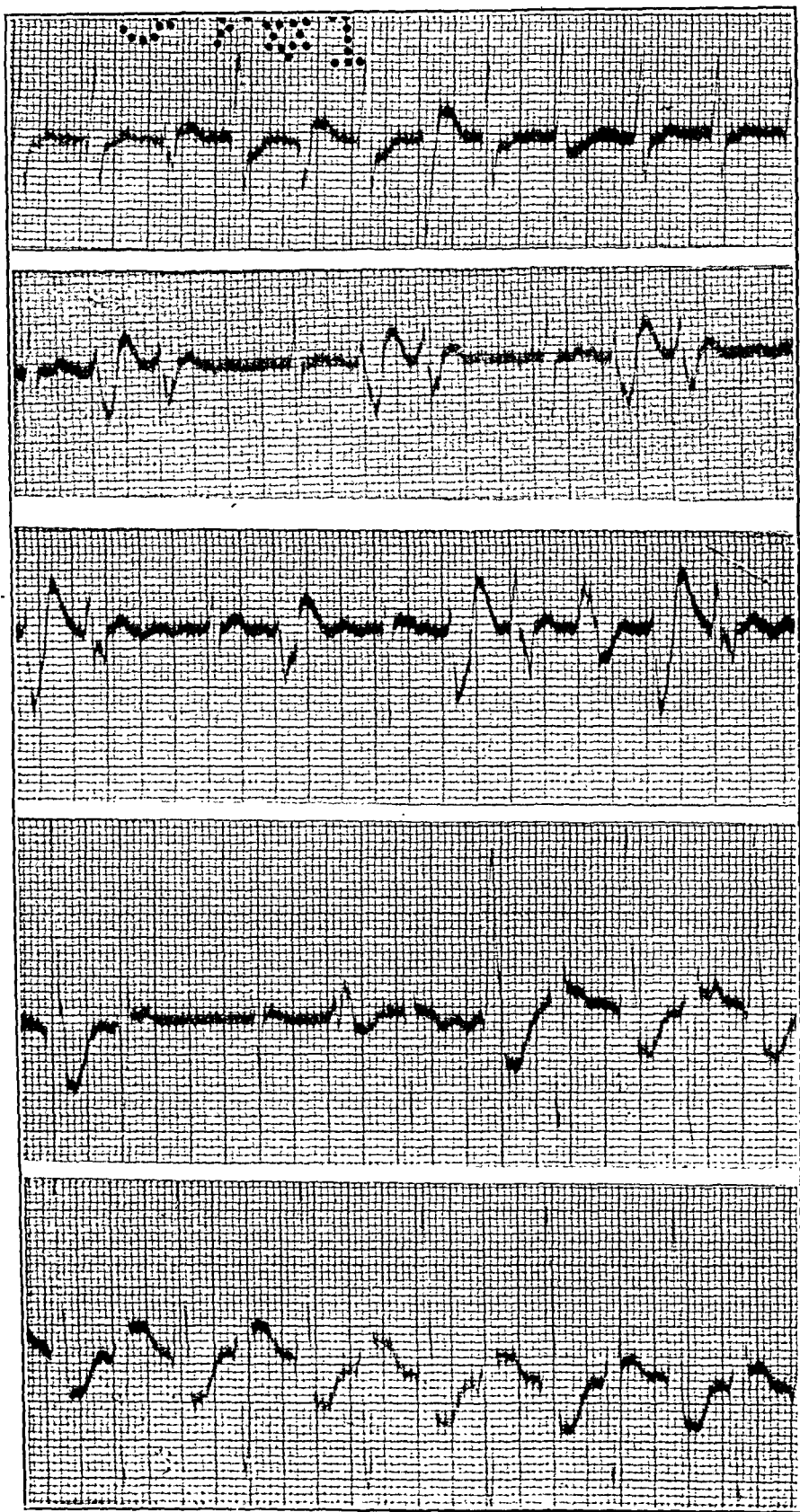


FIG. 3.—Record made March 23, 1921. Heart is beating very irregularly. Leads 1 and 2 show groups of extrasystoles different from the paroxysm, which is recorded in Lead 3. Leads 2 and 3 are each represented by 2 records.

Levy in experiments with chloroform vapors obtained a similar record.

In paroxysmal tachycardia of ventricular origin hitherto described, the site of the dominant rhythm has been in a single center in either ventricle; in the majority of the cases in the left ventricle. In our case, in order to cause this curious picture, as a result of a true ventricular extrasystole, we must assume that there are two independent foci, one in either ventricle, which initiate the contraction alternately in an orderly manner.

Ventricular types of extrasystoles are the more common forms of ectopic beats and in isolated cases may arise from more than one situation in the ventricles, occasionally in both ventricles in a given case. Succession of ventricular extrasystoles are uncommon,

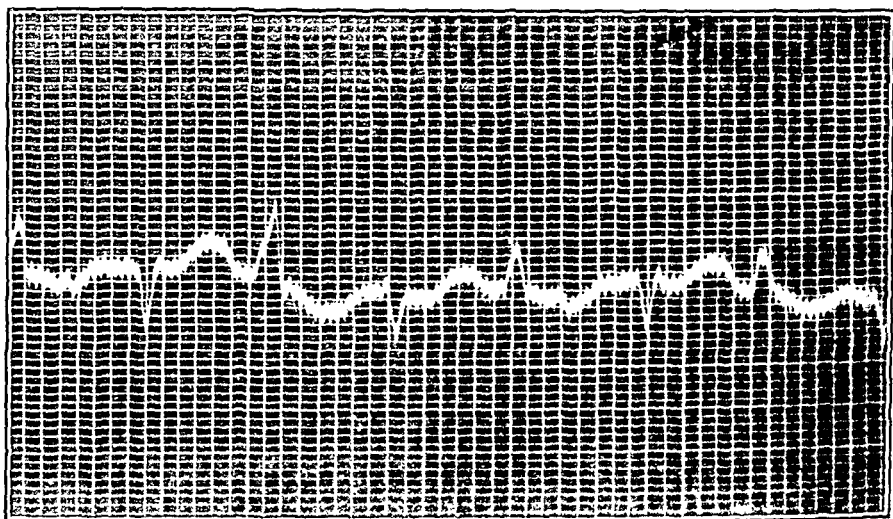


FIG. 4.—Lead 2 of a paroxysm of ventricular tachycardia induced in a cat following injection of .00234 gm. Strophanthin in oil. Cat died suddenly, immediately after record was obtained, August 18, 1922.

even from a single focus. It is extremely rare to encounter extrasystoles succeeding each other from both ventricles even for two beats. In a review of all the ventricular extrasystoles recorded at the Montefiore Hospital, such alternations occur in 2 cases out of a series of 35 ventricular extrasystoles. It is evident from the foregoing discussion that such an alternation of ventricular extrasystoles can occur, both clinically and experimentally but the continuous alternation for a long period is a very rare and unique phenomenon, only one other case so far having been reported. As stated above, the anomalous beats seen in our case preceding the paroxysm had all the appearances of ectopic ventricular beats, and arise in both ventricles; they are identical in form to those seen during the paroxysm, and as the auricles are in a state of fibrilla-

tion and cannot induce a paroxysmal tachycardia, it is unquestionably certain that we are dealing with a ventricular tachycardia.

The mechanism producing this alternation is problematic. A possible theory that suggests itself is that each ectopic center, because of the extreme rapidity of the impulse formation, alternately become exhausted and recovers; so that the pacemaker shifts sequentially in an orderly way from ventricle to ventricle.

Another mechanism which must be recognized as a plausible explanation, in such a case, is that we are dealing with a single focus giving rise to the paroxysm situated somewhere in the main stem of His's bundle, or perhaps, in the auriculoventricular node. Due to defective conduction through these stems of the bundle, the impulse starting the paroxysm is forced to travel down one of the branches. The next impulse coming on rapidly finds this refractory, as it has not had sufficient time to recover, the excitation wave takes the opposite branch and initiates a contraction. By this time the first stem has recovered and is again receptive, while the second branch is now exhausted and refractive; and so the impulse sways from side to side. Against this hypothesis, we must note that both the isolated extrasystoles and the deflections during the attacks have not the appearance usually ascribed to bundle-branch blocks. The time interval is short, only .08 second, and there are no aberrations. Furthermore, if these were levo- and dextrograms, the algebraic summation of the two should give rise to a normal ventricular deflection as presented by the patient. This was not found to be the case when the deflections in three leads were exactly plotted out according to the method described by Lewis.

**Conclusions.** We have presented a case of paroxysmal ventricular tachycardia in which the impulse travels alternately and regularly through each ventricle. Only one other case of a similar nature has so far been recorded. The mechanism of its production has been discussed. Digitalis intoxication is a possible cause in producing this serious arrhythmia. The danger lies in the transition of the paroxysm into ventricular fibrillation and sudden death.

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## COSTODIAPHRAGMATIC ADHESIONS AND THEIR INFLUENCE ON THE RESPIRATORY FUNCTION.

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By reason of its important anatomical relations and physiological functions, the diaphragm ranks second only to the heart among muscular structures. Its origin from the lower six ribs and their cartilages, the ensiform cartilage and the upper lumbar vertebrae and its insertion, after a dome-like course, into the central tendon, determine the piston action, by which its contraction increases the vertical diameter of the thorax. The dome of this fibromuscular septum is maintained through the negative intrapleural and the positive intraperitoneal pressures. The arc of the dome remains relatively constant in all phases of respiration (except forced inspiration) because of the compensatory changes in pressure upon either side and the moulding of the dome to the underlying liver and spleen.

The share of the diaphragm in respiration has been a mooted point for many years. Obviously, the ascent of the ribs upon inspiration, which leads primarily to an increase in the antero-posterior and lateral diameters of the chest, would appreciably decrease the vertical diameter were it not for the downward sweep of the contracting diaphragm. Its origin from the lower six ribs leads to their fixation on descent of the diaphragm. Fick<sup>1</sup> held that the ascent of the ribs occurring simultaneously with descent of the diaphragm creates an illusion of much greater movement in the latter than actually occurs. Upon this ground alone, he maintained that the inspiratory importance of the diaphragm had been greatly exaggerated. Hutchinson,<sup>2</sup> in discussing his remarkable paper upon vital capacity, expressed the opinion that "ordi-

nary breathing in men was entirely abdominal or diaphragmatic, but the contrary in deep breathing." He felt that inward movement of the anterior abdominal wall upon deep inspiration precluded downward movement of the diaphragm. Sewall and Pollard<sup>3</sup> presented a series of separate vital capacity readings for costal and diaphragmatic respiration in the same individuals. The physical difficulties encountered and the methods of control were not stated. They concluded that the vital capacity of costal breathing is greater than that of diaphragmatic breathing, thus accounting for the increase in the costal type with sudden respiratory stress. Fluoroscopical control of such experiments would seem imperative; under any circumstance, the existence of even normal diaphragmatic tonus would vitiate so-called uncomplicated costal respiration figures.

Expansion of the lower lobes and the dorsal portion of the upper lobes is admittedly dependent upon diaphragmatic contraction.<sup>4</sup> Furthermore, Meltzer<sup>5</sup> showed that intrapleural negative pressure in rabbits increased as the diaphragm was approached. He also determined that changes in intrapleural negative pressure upon inspiration were first and most felt at the base. From these observations, Meltzer divided the lung into surfaces of direct and of indirect expansion. Expanding force would obviously be exerted more markedly on surfaces of direct expansion. Interesting substantiation of this point might be derived from Keith's<sup>4</sup> quotation of Oppel's figures upon the greater dimensions of the basal infundibula (to use the former's obsolete nomenclature), as compared with the apical infundibula, could these data be confirmed in the original source. Unfortunately, reference to Oppel<sup>6</sup> reveals no corroborative figures. (Three years old: Apical infundibula, 0.12 mm.; basal infundibula, 0.38 mm. in diameter. Seventy years old: 0.45 mm. for the apical and 0.85 mm. for basal.) However, Oppel has included identical measurements under Rossignol's tables of dimensions for the different parts of the individual infundibulum ("fundus" and "münding").

Attempts to accurately estimate the part played by the diaphragm in respiration have followed certain mathematical lines. Fick<sup>1</sup> has pointed out that the diaphragm moves 1.5 cm. in quiet respiration and 3 cm. on forced inspiration. Keith<sup>4</sup> determined an area of 250 sq. cm. of the diaphragm to be in contact with the lungs. In this event, a descent of 10 mm. in the diaphragm would increase the thoracic space by 250 cc. Keith concluded that if 400 cc. be taken as the normal tidal air, the diaphragm must be considered a large factor in quiet respiration. Hultkrantz<sup>7</sup> determined a sweep of 10 cm. between the levels of the diaphragm on forced inspiration and forced expiration. He divided the respiratory responsibility of a 490-cc breath into 320 cc from the thoracic movement and 170 cc from the diaphragmatic descent.

From any angle, it must be apparent that the diaphragm plays a considerable part in respiration. Yet not until Hoover<sup>8, 9</sup> published his convincing observations upon the activation of the diaphragm was this important structure studied clinically to any degree. The methods of approach to its accurate study are several. The forward thrust of the abdomen upon inspiration has long been considered a measure of diaphragmatic activity. Litten's phenomenon demonstrates clearly the inspiratory descent of the diaphragm. The shape of the dome of the diaphragm may be determined by observation of the changes in the subcostal angle upon inspiration. Opposing the time-honored conclusion of Duchenne,<sup>10</sup> Hoover clearly demonstrated that activation of the diaphragm induced inward movement of the hypochondria. The external intercostal muscles, by their bucket-handle influence upon the ribs, tend to widen the subcostal angle upon inspiration. The sum total of the opposed actions of the intercostal muscles and the diaphragm on the costal margins is slightly in favor of the intercostals, so that with normal relations of the concerned parts there should be slight movement of the costal margins outward upon inspiration. This advantage is easily disturbed by changes in the position of the diaphragm, synechiæ or alterations in the muscular efficiency of either element in this delicate balance. Hence, an increasing importance must be accorded to observations of the changes in the subcostal angle upon respiration. Hoover utilizes this study in determining the form of the diaphragm rather than its gross function.

To these methods of study, based upon inspection, must be added the information gathered by palpation, percussion and roentgenological examination. Palpation will reinforce inspection in the above determinations and to them add the increase in extent of tactile fremitus determined by the increased vertical diameter of the thorax upon the descent of the diaphragm. Percussion will roughly gauge the movement of the diaphragm with respiration. Fluoroscopy is of paramount importance in studying the contour and the extent and regularity of movement of the diaphragm. Roentgenograms have a more limited field in determining the form and the position of this muscle.

Notwithstanding the development of our knowledge of and interest in phrenic function, but few contributions of a clinical nature have been added to the literature. Notable among these have been the roentgenological studies of Pryor.<sup>11, 12</sup> By careful fluoroscopical and radiographical observations, diaphragmatic immobility was determined in 53 out of 83 individuals, who had suffered from empyema or pleurisy with effusion, and some restriction of motion was determined in an additional 17. From the etiological standpoint, he found empyema gave the gravest prognosis, 34 of 47 cases studied developing complete unilateral immo-

bility; but pleurisy with effusion showed the same impairment of function in 9 out of 16 cases. Pryor concluded that a diaphragmitis with consequent infiltration, loss of elasticity and muscular atrophy or possibly phrenic neuritis constitute more probable causes of this disabling sequel than do diaphragmatic adhesions.

An unusual opportunity to study the effect of costodiaphragmatic adhesions upon the respiratory function has been afforded in the group of cases under consideration. In the main, they constitute the end-results of thoracic wounds and of empyema. With few exceptions, the routine examination of the diaphragm, as outlined above, was rigorously followed, especial stress being placed upon the study of the subcostal angles and upon fluoroscopy. As a measure of "mobility of the parts concerned in the breathing act,"<sup>2</sup> spirometric readings were made in each instance. The standards based upon height, Hutchinson<sup>2</sup> and Peabody and Wentworth,<sup>13</sup> have been superseded by those derived from body area. The most exhaustive work upon this phase of vital capacity is that of Dreyer,<sup>14</sup> but after a careful analysis of the available standards, West<sup>15</sup> concluded that the average vital capacity for the male is 2.5 liters per square meter of body surface, and for the female 2 liters per square meter of body surface. In this study, West's figures have been used as standard.

Except as otherwise noted in Table I, the diaphragm was totally immobile in all cases. The typical deformity is indicated in Fig. 1. Particular attention is directed to the vital capacity figures, ranging from 57.2 per cent of normal to 75.6 per cent (excluding Case IV), with an average (including Case IV) of 68.1 per cent. Pryor's conclusions of an actual paralysis of the diaphragm was disproved by observations of the movements of the costal margins in this group. Invariably, there was either slight movement of the costal margins toward the midline or no movement whatever upon inspiration. Hoover ascribed this phenomenon to the mechanical advantage of a more direct line of phrenic contraction. In effect, the points of origin and insertion of the diaphragm have been approximated more closely and the arc of contraction effaced by obliteration of the costophrenic sulcus through adhesions. This evidence of an ascendancy of the diaphragm over the intercostal muscles in their action upon the costal margins is proof of phrenic contraction. Then, too, in event of unilateral paralysis, the affected leaflet should be elevated upon inspiration because of the unopposed increase in abdominal pressure from descent of the intact leaflet. In no case was this balance movement noted.

For comparison with this group of complete unilateral diaphragmatic immobility, a second group of 6 cases with impaired mobility was collected. The wide fluctuations in vital capacity readings (71.7 to 102.2 per cent) in such a limited number of cases vitiate their significance. However, the average reading was 87.6 per cent of normal.



TABLE I.—INCLUDING CASES OF PRACTICALLY COMPLETE UNILATERAL DIAPHRAGMATIC IMMOBILITY.

Case.	Roentgenray findings.	Body area.	Vital capacity.	Per cent normal. (West.)
I. Influenza-empyema (thoracotomy)	Complete obliteration costophrenic sulcus	1.7	2550	60.0
II. Influenza-empyema recurrent (thoracotomy)	Diaphragm adherent to seventh rib laterally	1.9	2750	57.8
III. Influenza-tuberculosis (pneumothorax)	High adhesion diaphragm; pneumothorax, partial	1.8	3375	75.0
IV.* Influenza-empyema (thoracotomy)	Diaphragm adherent to eighth rib; sulcus obliterated; central dipping	1.8	4000	88.8
V. G. S. W., rt. shoulder, empyema (thoracotomy)	Complete obliteration costophrenic sulcus	1.85	3500	75.6
VI. Influenza-empyema (thoracotomy)	Costophrenic sulcus obliterated	1.55	2375	61.2
VII. G. S. W. (sucker) empyema (thoracotomy)	High diaphragmatic adhesions; obliterated sulcus; little central movement	1.75	3200	73.1
VIII. G.S.W., penetrating empyema (thoracotomy)	High adherent diaphragm	1.85	2650	57.2
IX. G. S. W.—T. and T. (thoracotomy)	Obliteration costophrenic sulcus with little motion	1.65	2400	58.1
X. G.S.W., penetrating (thoracotomy), retained F. B.	Small partial pneumothorax; obliterated sulcus, little motion	1.8	2900	64.4
XI. G.S.W., penetrating (thoracotomy)	High adhesion diaphragm; narrow sulcus, little motion	1.8	3400	75.5
XII. G.S.W., penetrating (F.B. retained)	High adhesion diaphragm; narrow sulcus, central flattening	1.9	2950	62.1
XIII. G.S.W., penetrating (thoracotomy)	Obliterated sulcus	1.65	3000	72.7
XIV. G.S.W., sucker (thoracotomy) pneumonia-empyema	High adhesions diaphragm; obliterated sulcus	1.95	3500	71.7
XV. G. S. W.—T. and T. (thoracotomy)	Obliterated sulcus	1.75	3000	68.5

From the data advanced, costophrenic synechiæ, obviously, constitute a considerable embarrassment to respiration. A reduction of 31.9 per cent in vital capacity while a serious respiratory handicap, is probably still an inadequate measure of the respiratory interference of unilateral fixation of the diaphragm; for the existence of any degree of tonus in the fixed muscle will have reduced the handicap somewhat by aiding inspiration. Further—

\* Case IV is an interesting commentary upon the efficacy of continued conscientious breathing exercises. Of an athletic type this individual has practised forced or opposed breathing daily for the past three years.

more, compensatory intercostal effort upon the side of the fixed diaphragm and contralateral increase in both intercostal and diaphragmatic activity are to be anticipated on fixation of one diaphragmatic leaflet by adhesions. Therefore, the percentage reduction in vital capacity, above stated, has been favorably influenced by other factors, and the actual uncompensated decrease would be greater.

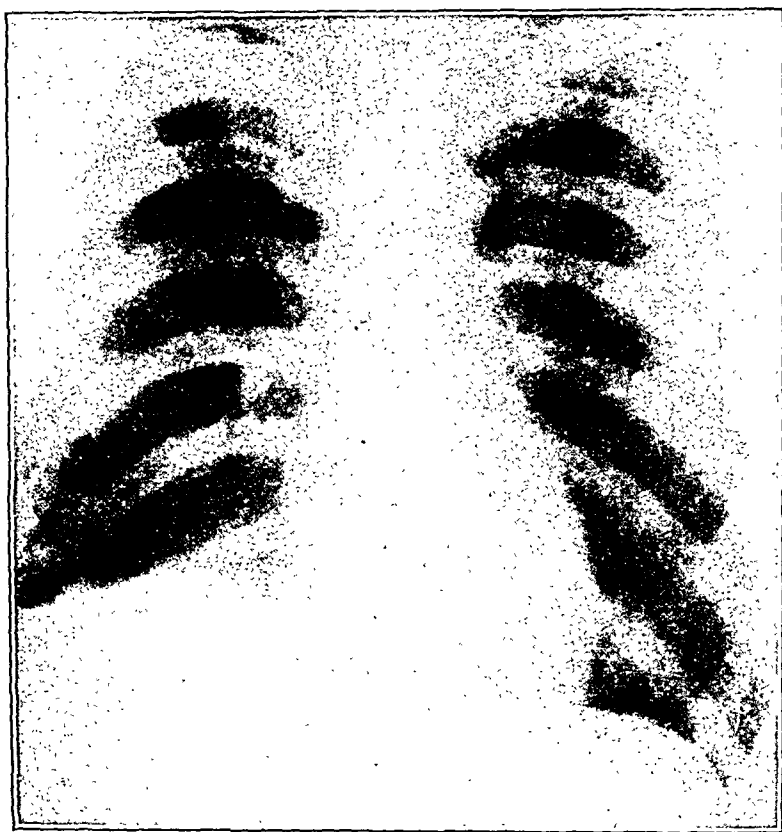


FIG. 1.—Typical phrenic deformity.

**Conclusion.** It would seem apparent that the part of the diaphragm in deep respiration has been underestimated. From the present vital capacity studies, which clearly minimize the actual influence of a unilateral fixation of the diaphragm upon respiratory function, the normal diaphragmatic contraction must account for at least 60 per cent of the respiratory interchange in deep breathing. Tidal-air observations are impossible in the human; but the recent work of Drinker, Peabody and Blumgart<sup>16</sup> suggests the possibility of determining, by animal experimentation, the influence of unilateral phrenoplegia and fixation on this phase of respiration.

Protection of the diaphragm from needless trauma and continued contact with inflammatory products will limit the occur-

rence of disabling costophrenic synechiae. Lastly, avoidance of protracted diaphragmatic immobility is essential for a complete restoration of function. Early and continued breathing exercises are advised in all cases of pleural inflammation involving the diaphragm.

NOTE.—Since this paper was submitted for publication, Hoover has reported the results of his studies on the action of the intercostal muscles, in the *Journal of the American Medical Association*, 1922, 30, 1. One finding in particular is of interest in relation to the present work. Hoover induced a pronounced hyperpnea in experimental dogs by having them breathe an atmosphere rich in carbon dioxide (25 per cent). On phrenic section in such animals a reduction in vital capacity of 50 per cent was remarked. This finding would be most significant, if it were found constant by repeated experiments, even though subsequent laparotomy determined in the instance reported above, contraction of the crura.

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### THE DIAGNOSIS OF TUBAL PREGNANCY.

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THERE are many cases in which the clinical picture presented by extrauterine pregnancy is so classical that its diagnosis is almost compelling. In others, again, its recognition before operation is exceedingly difficult, in spite of the most careful study of the patient's history and the most thorough physical examination. Even when the diagnosis seems quite clear, the surgeon not infrequently meets with surprises on opening the abdomen, for, as will be discussed below, there are a number of other conditions which

may almost perfectly mimic the clinical picture of this disease. On the other hand, even more frequently operation reveals extrauterine pregnancy in cases in which its existence had not even been thought of. The general practitioner or the gynecologist who would avoid too many humiliating surprises of this sort must have the possibility of this condition constantly within his field of vision.

The diagnosis of extrauterine pregnancy is usually considered under two heads, viz.: (1) The diagnosis before rupture and (2) the diagnosis after rupture. This plan does not appeal to me as a very wise one, for small and perhaps repeated ruptures of the pregnant tube often occur with such slight symptoms as to defy recognition. Indeed, it is relatively rare to operate upon cases in which there has been no internal hemorrhage whatsoever, either from rupture of the tubal wall or from tubal abortion, and even more rare to operate before at least some intratubal bleeding.

The clinical picture in the unruptured cases, or in those with moderate intraperitoneal bleeding, is quite different from that characterizing those cases in which the internal bleeding is sudden, overwhelming, and cataclysmic. For this reason, it would seem wiser to group the cases, from the standpoint of diagnosis, into (1) the nontragic type—those with moderate internal hemorrhage or none at all; and (2) those of the tragic or cataclysmic variety, where hemorrhage is sudden and perhaps overwhelming. I may say that in this brief paper I shall not attempt to discuss the less common forms of extrauterine pregnancy, nor shall I consider the diagnosis of such sequelæ as secondary abdominal pregnancy, lithopedion formation, etc. Moreover, I shall not enter into any discussion of the histological diagnosis of tubal pregnancy.

1. THE NON-TRAGIC TYPE. It is in this group of cases that the problem of diagnosis is often most confusing. Patients of this type are often in good general health and not confined to bed. The principal points of diagnostic importance may be briefly summarized as follows:

(a) *Menstrual Irregularity.* It was formerly stated that as a rule one or more menstrual periods, usually one, are skipped, following which uterine bleeding begins and is kept up more or less constantly. My own experience, however, like that of a number of recent authors, has been that menstruation is not skipped at all in a large proportion of cases. In Farrar's cases<sup>1</sup> only 34 per cent showed an amenorrhea. This is the same figure given by Wynne<sup>2</sup> in his exhaustive study of 303 cases from the Gynecological Clinic of Johns Hopkins Hospital. Other authors, however, put the figure much higher (MacKenzie<sup>3</sup> at 75 per cent, Rongy<sup>4</sup> at 71 per cent). It is not uncommon to find that the menstrual period is actually anticipated by from a few days to perhaps even two or three weeks.

Perhaps even more characteristic than the short period of amenor-

rhea which often occurs, is the uterine bleeding which then puts in its appearance. Most often the bleeding is scanty and "spotting" in type, and is associated with crampy pains in one side or the other of the lower abdomen. Rarely is the hemorrhage free, and almost never alarming. This is a point of some diagnostic importance in the differentiation between tubal pregnancy and incomplete abortion of a uterine pregnancy. In the latter, as is well-known, bleeding may be exceedingly free, so that the patient may soon be almost exsanguinated. This is almost never the case with the external bleeding of extrauterine pregnancy. Some authors lay stress upon the abnormal brownish color of the bloody discharge seen with extrauterine pregnancy, but I do not believe that this sign will often prove of value.

Bleeding of the type described is an almost constant symptom with ruptured tubal pregnancy. It was present in 67.4 per cent of Farrar's cases. In a rather large experience I have seen only a few cases in which this symptom was lacking. In one of these, a patient referred by Dr. B. S. Rankin, of Tunnelton, W. Va., there had been complete amenorrhea for two months, after which the patient began to suffer with violent pains in the left iliac fossa, associated with syncopal attacks. A large sensitive mass filled the left side of the pelvis at the time of operation. A diagnosis of ruptured left tubal pregnancy was made, in spite of the absence of uterine bleeding. This was confirmed at operation. Six weeks after the operation the patient expelled a three months' fetus from the uterus. It had been a case of combined intra- and extrauterine pregnancy, the uterus being pregnant at the time of removal of the tube. There can be no doubt that the presence of the live fetus in the uterus was the explanation of the absence of uterine bleeding. In two other cases, which I have previously reported, the fetus was apparently alive at the time of operation. To put it conversely, I believe that the death of the fetus is the responsible factor in the causation of the uterine hemorrhage.

This is the logical explanation if one recalls the mechanism of normal menstruation. The corpus luteum, through its internal secretion, calls forth the characteristic hypertrophic changes seen in the endometrium just before menstruation. It has nothing to do, however, with the actual bleeding of menstruation, which does not begin, as a matter of fact, until the influence of the corpus luteum is inhibited or counteracted by some other factor—most likely the death of the ovum which was thrown off at the preceding ovulation. There are other facts which point to the death of the unimpregnated ovum as a cause of the bleeding of normal menstruation and to the death of the impregnated ovum, *i. e.*, the fetus, as a cause of the bleeding in either intra- or extrauterine pregnancy.

Certainly this theory is more plausible than that recently suggested by Polak,<sup>5 6</sup> who believes the hemorrhage is the result of

"ovular unrest" caused by hemorrhage around the ovum in the tube, and that the tubal peristalsis thus excited is transmitted to the uterus, thus disturbing the decidua and causing bleeding. Cases like the three mentioned above in this paper as being unaccompanied by hemorrhage would seem to be sufficient refutation of this theory. In all of these there was certainly sufficient distention of the tube to excite peristalsis, and yet there was no bleeding, even in the case where there was an associated intrauterine pregnancy.

(b) *Pain.* With few exceptions pain is a prominent symptom, usually the most prominent symptom, in cases of tubal pregnancy. Its frequency as a symptom is put variously at from 80 to 96.6 per cent of all cases. The explanation of the pain is no clearer than our still imperfect knowledge of the mechanism of pelvic pain in general. Whether it be due to increased tubal peristalsis or to the congestion of the parts, whether the pain stimuli are perceived in the tube itself, or whether they are really referred to the somatic nerves of the parietal wall, according to the segmental theory of Head—these are still points, concerning which we cannot speak dogmatically. There is a little reason to doubt, however, that the sudden attacks of colicky pain associated with faintness or actual syncope are the result of ruptures and internal hemorrhages of varying degrees of severity. Here the pain and the faintness are perhaps both in large measure due to the contact of the escaping blood with the peritoneum.

Broun,<sup>7</sup> in an interesting comparison of the history and the operative findings in cases of tubal pregnancy, found in a series of 55 cases, that 22 in which there was a history of sharp severe pain showed at operation an escape of free blood into the peritoneal cavity. In another group of 20 cases the pain was chiefly pelvic, and was described as varied in character and degree. In these the blood in the pelvis was found to be encapsulated. In still another group of 7 cases, the only pain was a slight discomfort in the involved side, and here there was no extratubal bleeding at all. These findings are practically similar to those of Farrar, who states that "in only 18.8 per cent of cases was the pain of the character ordinarily considered peculiar to ectopic gestation. In the remaining cases it was not to be differentiated from that of any severe pelvic lesion."

(c) *Findings on Pelvic Examination.* The demonstration of a one-sided mass in the pelvis is little less than a *sine qua non* in the diagnosis of tubal pregnancy. There is a small proportion of cases where the suspicion is strong in spite of the absence of this finding, but here great caution is necessary to avoid embarrassing mistakes. Farrar found a unilateral pelvic mass in no less than 96 per cent of her cases, and other authors (Frank, Oastler) give percentages almost as high. The usual statement is that the mass is exquisitely tender. My own experience has been that there are not infrequent

exceptions to this rule, and that in a certain number of cases the mass is not any more tender than many of those encountered in connection with pelvic inflammatory disease.

Enlargement of the uterus is usually slight or perhaps not discernible at all. On the other hand, when the uterus is much enlarged the existence of intrauterine pregnancy may be reasonably assumed.

(d) *Other Symptoms.* While the signs and symptoms already described are those upon which the diagnosis of extrauterine pregnancy will usually depend, there are a number of others which not infrequently throw considerable light on the individual case. For example, the subjective symptoms of pregnancy are often observed by the patient, more especially before the occurrence of rupture of the gestation sac. Often, however, they are only slightly or not at all noticeable. This applies to such symptoms as nausea and vomiting, increased frequency of urination, etc. The previous history of the patient is often suggestive, especially if she has apparently become pregnant after a long period of sterility. One child sterility especially is apt to be followed by tubal pregnancy. About 30 per cent of all cases of the latter, according to MacKenzie, give such a history. The explanation of this predisposition is simple enough when one recalls the frequency with which tubal inflammation is lighted up by pregnancy, and the etiological importance of tubal obstruction in the production of tubal gestation. From the same point of view, considerable importance attaches to a history of previous pelvic operations, because of the frequency with which these cause mechanical obstruction of the tube lumen by external adhesions or obliterative inflammatory processes. The passage of bits of decidua is suggestive, but will scarcely permit of differentiation from intrauterine pregnancy with abortion. Besides, this occurrence is not observed in the great majority of cases.

TRAGIC CASES. Fortunately, only a small proportion of all cases of tubal pregnancy—probably about 5 per cent—are encountered in the so-called tragic or cataclysmic stage. In these it is at times possible to elicit a history of one or more previous attacks of colicky pain, together with faintness or actual syncope, indicating perhaps repeated smaller hemorrhages before the real deluge. In other cases the patient has had little or no previous warning, having perhaps noted only a slight amount of abnormal uterine bleeding and a moderate discomfort in one or other lower abdominal quadrant. With the sudden onset of massive hemorrhage there occurs a sharp lancinating pain in the involved side of the pelvis, weakness, syncope, extreme pallor, rapid thready pulse, a cold clammy skin, sighing respiration, etc.—in short, all the classical symptoms of alarming internal hemorrhage. Frequently the abdomen becomes full and rounded, especially in women with lax abdominal walls. Contrary to Schumann and DeLee, I have quite frequently been able to elicit dulness in the flanks on percussion.

In cases in which the patient is not seen until the lapse of a good many hours, careful inspection of the umbilicus will often show the presence of the "blue belly-button sign" of Cullen.<sup>8</sup> I have fully discussed and pictured this important sign in a recent article in the Journal of the American Medical Association.<sup>9</sup> It was first described by Cullen in 1919. Its presence makes the assumption of intra-abdominal hemorrhage highly probable. It is of course not pathognomonic of ruptured extrauterine pregnancy, as I took pains to emphasize in my original article. In addition to the 2 cases reported in the latter I have since then observed the sign in two other patients in whom operation disclosed ruptured tubal pregnancy. Where there is a history of menstrual irregularity, sudden unilateral pelvic pain, with symptoms of internal hemorrhage, either with or without the presence of a definite pelvic mass, the demonstration of Cullen's sign makes the diagnosis of ruptured tubal pregnancy almost absolutely certain. In view of the probable cause of this sign—lymphatic absorption of blood pigment—it is obvious that it may in exceptional cases occur in association with other conditions. But this does not militate against its importance as a diagnostic sign in cases where there are other symptoms suggestive of ruptured extrauterine pregnancy. It is true that in most of these the diagnosis can be made with reasonable certainty without the aid of Cullen's sign, but at times the picture is not so clear-cut, and one is grateful for every ray of light that can be thrown on the problem. I make this explanation because one or two authors, apparently under the erroneous impression that the sign had been described as pathognomonic of ruptured extrauterine pregnancy, have taken the trouble to report cases illustrating the obvious fact that occasionally it may occur with other conditions.

The blood picture in cases of the tragic type is often of importance in diagnosis. Where the hemorrhage is severe, there is usually a high leukocytosis, which develops very soon after the onset of the bleeding. The hemoglobin percentage is of course diminished, but the figure can in no way be considered as an index of the amount of bleeding, inasmuch as it requires many hours for the hemoglobin to drop to its lowest point, as Schumann<sup>10</sup> has emphasized.

**Differential Diagnosis.** It is of course possible to mistake extrauterine pregnancy for any one of a multitude of other pelvic or abdominal conditions, and *vice versa*. There are only a few, however, in which this problem of differentiation presents itself with great frequency, and I shall therefore discuss only the two or three which would seem to be of greatest practical importance in this connection.

*Threatened or incomplete abortion of uterine pregnancy.* Perhaps the greatest number of diagnostic errors are made in the differentiation between tubal pregnancy and abortion of normal intrauterine pregnancy. This distinction is obviously of the greatest



importance, because of the very different therapeutic procedure called for in the two conditions. It may be a serious thing to curette, and merely to curette, a case of tubal pregnancy, and likewise it would be unfortunate to subject a patient to laparotomy in a case of simple miscarriage. In either case a patient may give a history of skipping one or more periods, and then beginning to bleed more or less continuously. There may be pain with a miscarriage, but it is less severe than with an ectopic pregnancy, and is rarely unilateral. The diagnosis is, after all, dependent upon the pelvic examination. In the case of a threatened miscarriage, after the first few weeks of pregnancy the uterus is apt to be much larger than with an ectopic. However, in cases of incomplete abortion where the uterus has almost emptied itself, the organ may show little or no enlargement, as with ectopic pregnancy.

Most important of all is the finding of a unilateral tender mass with ectopic gestation and the negative finding in the adnexa with normal pregnancy. In most cases the distinction is thus easily made, but it is at times more difficult, as in very stout or very nervous women. It is not surprising, therefore, that many mistakes of diagnosis have occurred. Not a few women have been subjected to laparotomy unnecessarily, while on the other hand in many cases curettage has been performed in cases of extrauterine pregnancy, with sad results. I recall rather vividly a comparatively recent case in which I was called upon to open the abdomen of a woman who had, a few hours previously, been curetted for what had been presumed to be an early miscarriage. After the curettage the woman's pulse became rapid, her skin became pale, and, in short, she quickly developed symptoms of alarming internal hemorrhage. This impression was confirmed by the operation, for the abdomen was full of blood. The source of the latter was a tubal rupture, evidently caused by the trauma of the curettage. The patient barely escaped with her life. The same danger of rupturing the gestation sac must be borne in mind in making the usual examinations, especially under anesthesia, when the protective rigidity of the abdominal wall is done away with. There are few teachers of gynecology who cannot recall such mishaps as a result of pelvic examinations made by students.

*Acute Pelvic Inflammatory Disease.* In cases of acute salpingitis, especially of the gonorrheal type, there is a tendency for a suppression of the menstrual function. Usually one period is thus skipped, and then, after a period of a number of days, uterine bleeding puts in an appearance. Pelvic pain is the rule, and it may be much more severe on one side than the other, while bimanual examination may show a one-sided mass, where the involvement is still confined to one side. It will thus be seen that the picture of ectopic pregnancy may be very closely simulated.

As a rule the diagnosis is made possible by the history of a possible

gonorrheal, postabortive or puerperal, infection, by the existence of a much higher fever with the inflammatory disease than is common with ectopic pregnancy, or by the fact that the pelvic masses are bilateral, as they usually are with inflammatory disease. When bleeding is present with salpingitis, it is rarely associated with sudden attacks of faintness, as with ectopic pregnancy, and there is no history of subjective signs of pregnancy. Such points of differentiation will as a rule enable one to make a correct diagnosis, but in a certain proportion of cases the distinction between the two conditions is very difficult, and mistakes frequently occur.

*Ovarian Cysts* (especially corpus luteum cysts). As a rule, ovarian cysts are not likely to be confused with tubal pregnancy, inasmuch as, with the exception of corpus luteum cysts, they do not usually give rise to the menstrual disturbance and the pain so characteristic of the latter. I have seen a number of cases in which mistakes in diagnosis were made because of the coexistence of intra-uterine pregnancy and unilateral ovarian cysts. The occurrence of abortion in such a case will create a clinical picture which is at times almost indistinguishable from tubal gestation—pain, uterine bleeding following amenorrhea, a unilateral pelvic mass, etc. Examination under anesthesia will often help materially in settling the question, permitting of easier outline of the usually ovoid, nicely circumscribed ovarian cyst. Curettage, of course, is of decisive importance. The gross or microscopical recognition of placental elements is proof positive of intrauterine pregnancy.

It is the corpus luteum cyst, however, which is of the greatest interest and the greatest importance in this connection, for it is this variety which is especially apt to simulate almost perfectly the clinical picture of ectopic gestation. There is still much to learn concerning the relation of the corpus luteum cyst to the corpus luteum of menstruation and the corpus luteum of pregnancy. Certainly it would seem fairly clear that the function—or at least one of the functions—of active lutein cells is to inhibit menstrual bleeding, although they are responsible for the premenstrual or pregravid hypertrophic changes in the endometrium. It is hence not surprising that the corpus luteum cyst, with its lining of lutein cells, often causes a period of amenorrhea. Only a single period is usually missed, and then in from a few days to a few weeks, there begins an irregular uterine hemorrhage, which like that of ectopic pregnancy, is usually scanty in amount and perhaps associated with some pain. Added to this is of course the presence of an enlargement in one side of the pelvis. It is easy to understand, therefore, why mistakes in diagnosis have often occurred.

*Other Conditions.* Occasionally, the clinical picture of ruptured extrauterine pregnancy is almost exactly reproduced by intra-abdominal hemorrhage from a corpus luteum or a follicular cyst. I reported a striking case of this type in 1917,<sup>11</sup> and collected 84

similar cases from the literature. Since then a number of other instances of this occurrence have been recorded, so that, in spite of its comparative rarity, its possibility should be borne in mind.

There are a number of other conditions which may at times be confused with tubal pregnancy—appendicitis, ovarian cyst with twisted pedicle, etc. With these, however, the differentiation is as a rule easier than with those which have been considered, so that they may be passed with mere mention.

**Summary.** 1. The diagnosis of tubal pregnancy is at times exceedingly easy, at other times very difficult or perhaps impossible.

2. Diagnosis will be most frequently made by those practitioners who are constantly on the alert for it.

3. The conditions from which tubal pregnancy, of the non-tragic type, is most frequently to be differentiated are pelvic inflammatory disease, threatened or incomplete abortion of an intrauterine pregnancy, and unilateral ovarian cysts, especially of the corpus luteum variety.

4. The most important diagnostic symptoms are the menstrual history, the pelvic pain and the presence of a unilateral tender mass in the pelvis.

5. The diagnosis of the tragic or cataclysmic cases is as a rule comparatively simple. At times it may be difficult or impossible to distinguish cases of this group from the occasional instances of intra-abdominal hemorrhage due to the rupture of a corpus luteum or follicular cyst. More rarely they are mistaken for such conditions as acute appendicitis, ovarian cyst with twisted pedicle, etc. The "blue belly-button" sign of Cullen is often of value in the recognition of intra-abdominal hemorrhage, which is most often due to ruptured ectopic pregnancy.

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## THE ALKALI RESERVE OF THE CEREBROSPINAL FLUID IN VARIOUS STATES OF THE CENTRAL NERVOUS SYSTEM.

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THE intimate relation of the cerebrospinal fluid and the tissues of the brain and cord suggests that a study of the chemistry of the fluid may throw some light upon the physiology and pathology of states of the central nervous system. The present paper, which deals with the relation of the carbon-dioxide combining power of the cerebrospinal fluid to various symptoms, signs and diseases, is based upon a study of 110 cases, with 156 analyses of cerebrospinal fluid and 62 of the blood, from patients in the Cincinnati General Hospital.

*Material and Methods.* The specimens of spinal fluid and blood were collected during the course of the clinical study of each case. The cerebrospinal fluid was obtained by lumbar and cistern puncture and the blood from the arm veins. Several methods of collection and preservation were tried. In most cases the examination was made within fifteen minutes. In others the test-tubes were plugged with rubber stoppers and put in the ice-box. Some specimen tubes were plugged with cotton stoppers only. The best method was found to be to cover the freshly drawn spinal fluid with sterile liquid petrolatum to a depth of 2 to 3 cm. Cell counts were always made on freshly drawn fluid. The oil method preserved the original reaction and alkali reserve for long periods, especially when kept on ice. Fluids preserved with toluol showed the same alkali reserve for weeks unless the glass tubes were very soluble. For determining the reaction to phenolphthalein or phenolsulphonaphthalein, the freshly drawn fluid, or that drawn under oil, was used. The carbon-dioxide combining powers of the spinal fluid and of the blood plasma were determined by the method of Van Slyke, using the mercury burette. Clinical observation as well as the chemical analyses, except the Wassermann tests, were made by the author, so that the technic in each case was uniform and of value for purposes of comparison.

For fractional analysis, 2 to 5 cc (occasionally more) were collected in separate tubes, the tubes being numbered in the order in which the fluid came out. The term "lowest fraction" is used to indicate the first fluid that came out.

*Data.* In the study of the fluids, it was found that in some cases the first fluid withdrawn differed from the succeeding fractions, indicating that the carbon-dioxide combining power differed in the fluid surrounding different regions of the brain and cord. The

following two tables show the results when the first fraction (usually the first 5 cc) was used. The results of the fractional analysis are given later.

TABLE I.—CARBON-DIOXIDE VOLUMES PER CENT IN SPINAL FLUID AND BLOOD PLASMA.

	Spinal fluid.			Blood plasma.			Blood plasma relation to spinal fluid.		
	No. of cases.	Range.	Av. vol. %.	No. of cases.	Range.	Av. vol. %.	Higher.	Lower.	Similar.
Mentally normal . . . . .	32	28-60	50.71	21	29-66	50.30	11	9	1
Unconscious . . . . .	19	11-65	39.50	8	32-68	47.62	3	4	1
Convulsions . . . . .	8	32-53	43.37	2	46-48	47.00	2		
Delirium, mania . . . . .	6	34-55	41.66	1		39.00	1		
Headache . . . . .	10	1-52	38.90	5	32-60	46.20	3	1	1
Semicomatose, hazy, drowsy . . . . .	44	6-79	41.58	18	33-56	46.70	11	5	0

TABLE II.—CARBON-DIOXIDE VOLUMES PER CENT IN SPINAL FLUID IN RELATION TO VARIOUS TESTS.

	No. of cases.	Range.	Av. vol. %.
Wassermann negative* . . . . .	67	22-79	49.10
Wassermann positive† . . . . .	9	16-62	44.30
Globulin normal . . . . .	47	22-60	45.87
Globulin increased . . . . .	50	16-79	41.14
Pressure normal . . . . .	47	24-61	49.36
Pressure increased . . . . .	65	6-65	42.00
Cell count normal‡ . . . . .	24	36-60	48.50
Cell count above 8 . . . . .	54	16-79	43.10
Alkaline to phenolphthalein . . . . .	17	34-66	45.60
Acid to phenolphthalein . . . . .	35	23-55	38.80

\* Spinal negative, blood positive, 8 cases, both negative 37.

† Spinal positive, blood negative, 0 cases, both positive 7.

‡ The majority of those with a normal cell count occurred between 50 and 56 with the maximum at 51 and 52. The majority of the abnormals occurred between 33 and 56, with the maximum between 46 and 48. The cell counts varied at different levels; in one case (F 5932) the ventricular fluid showed 27 cells, while fluid from lumbar puncture showed 400 cells.

Only those fluids were recorded in these calculations which were taken under ideal conditions, without loss of carbon dioxide. The occurrence of fluids alkaline to phenolphthalein was unexpected in so large a proportion, but it was found that fluids at one level could be "acid," while at another level they could be alkaline to phenolphthalein. The following cases show some of the variations:

F 7955.—Lowest fluid acid to phenolphthalein, higher fluids alkaline. (Cerebrospinal lues, septicemia.)

F 5932.—Lowest fluid acid to phenolphthalein, higher fluids alkaline. (Tuberculous meningitis.)

In this case 1 cc of phenolsulphonephthalein solution injected into the ventricles. A lumbar puncture later showed the first fluid to be yellow and the later fractions pink. The yellow tube turned pink on addition of alkali, showing that the color was caused by the phenolsulphonephthalein and that the lowest portion was acid (below  $p^H$  7) and the upper portions were alkaline to this indicator.

F 8215.—Lowest fluid alkaline ( $CO_2$  combining power, 52); after 8 cc the fluid was intensely alkaline ( $CO_2$  combining power, 66). (Cerebrospinal lues.)

F 8823.—Fractions, totalling 25 cc, all acid to phenolphthalein.

F 8833.—(1) Fractions all acid, totalling 30+ cc. Later: (2) first 5 cc, just alkaline; third 5 cc, less alkaline; fourth 5 cc, very alkaline. ( $CO_2$  combining powers, 40–40–39; the most alkaline had a slightly lower carbon-dioxide combining power.) (Encephalitis lethargica.)

F 8885.—Lowest alkaline, middle acid, highest alkaline (5 cc fractions). (Carbon-dioxide combining power, 44–43–49.) (Cerebrospinal lues.)

F 9732.—Lowest fraction acid, highest alkaline (total 19 cc). (Skull fracture.)

F 9918.—Second 5 cc fraction slightly alkaline; fourth 5 cc fraction, acid. (Miliary tuberculosis.)

G 3031.—All fractions (total 50 cc) acid to phenolphthalein. They were alkaline to phenolsulphonephthalein, this degree being represented as follows: First 15 cc, +; second 15 cc, +++; third 15 cc, ++; fourth 5 cc, ++. (Miliary tuberculosis.)

F 9769.—Fluid obtained by cistern puncture was acid to phenolphthalein.

F 9151.—Fluids contaminated with blood usually were alkaline. Lowest 8 cc acid, highest 7 cc (of 15 cc) alkaline. (Two middle fractions had carbon-dioxide combining powers of 32, but the upper was alkaline and the lower acid.)

In 15 determinations in *encephalitis lethargica*, the average during the acute manifestations was 48.85, with a range from 37 to 79 in the fluid from the lowest part of the canal. Fluids from successively higher levels in one case showed 37–32–32–34–32 (portions of 5 cc each), with a difference of 5 volumes per cent between the lower and the upper 5 cc (a difference of 30 to 40 cc) in the spinal canal. Another determination showed 40–40–x–x–39 for the successive levels. There was some tendency for the highest fluid to have the lowest carbon-dioxide combining power. In a case in which the fluid (lowermost) was followed during three periods up to recovery, there was an increase in the carbon-dioxide combining power as the clinical condition improved: 38 during the acute stage, 41 during beginning convalescence and 58 on recovery.

In 22 cases of *uremia*, *uremia with cerebral hemorrhage* and *cardio-renal disease*, taking the lowermost fluid, the average for cardio-renal cases was 43.5 (range 22 to 54); for *uremia*, 43.5 (range 33 to 65); *uremia with cerebral hemorrhage*, 43.7 (range 6 to 63); and for *cerebral hemorrhage alone*, 45.4 (range 24 to 55). In a case of *uremia with cerebral hemorrhage*, fluid taken in successive parts gave 46 for the lowest, then 32-32-34, a variation of 14 volumes per cent. A cistern puncture in a case of *cerebral hemorrhage* gave 30 for the first fluid removed, and 6 for the final portion. In both of the cases, there was a reduction in the alkali reserve in the uppermost portions of the cerebrospinal fluid. A cistern puncture in another case of *cerebral hemorrhage* gave a fluid of 45 volumes per cent.

In 3 cases of *tetanus* studied, the range in the lowermost fluids was 50-52-53, the fluid being taken during the stage of acute manifestations.

The range in 5 cases of *cerebrospinal lues* was 43-44-46-31-52, with an average of 47.2. In 2 cases, where successive levels were studied, the figures were 52 for the lower level and 66 for a higher level in 1 case and 44-43-49 for successive levels in another case. Both showed a higher alkaline reserve in the higher fluid, differing from *cerebral hemorrhage* in this respect. Two cases of *luetie meningitis* gave 30 and 56 respectively. In *paresis*, the range was 1-47-50-51-52, the average reading being 50. In *tabes*, the range was 16 (*taboparesis*), 46 (*taboparesis*) 47-53-56-60, with an average of 52.4 (46.3, including the lowest reading).

In *meningococcus meningitis*, the average was 39; *tuberculous meningitis*, 41.35 (range 11 to 52 in 14 fluids); *streptococcus meningitis*, 23-32-32-20; *meningismus* in *pneumonia*, 39; *leptomeningitis* (*cerebral abscess*), 33-37-48. In *tuberculous meningitis* (*miliary tuberculous*) fluids from successive levels, starting with the lowermost, showed  $\text{CO}_2$  combining powers of 32, 35, 36, 35 and 37, 38, 37, 32. Fluids taken at separate intervals during the course of the disease showed in one case 50-48-47-11, in another 46-49-42-46-44, and a third 32-37. Another case of *miliary tuberculosis*, without meningeal symptoms, was 36. *Pulmonary tuberculosis*, 40-56.

Four cases of *acute alcoholism* showed 36-43-48-52, with an average of 44.74.

Some observations on *acute poisonings* were: Carbon monoxide, 56; *arsenobenzol*, 28-36; *morphinism*, 45-46; *hyoscine-morphine*, 61 (alkalies intravenously); *veronal*, 55; *impure whiskey*, 38-38; *methyl alcohol*, 48.

In 3 cases of *epilepsy*, the average was 44.6 (37-46-46-46-48). Observations upon fluid from three levels showed the same reading (46). Two cases of *skull fracture* showed 50-45; in the latter, fluid showed 40-39-43 volumes per cent of combined carbon dioxide.

In 2 cases of *hysteria*, the percentages were 42 and 49. A case

of *melancholia* was 38 and one of *paranoia*, 46. *Senile dementia*, 3 cases, 52-53-56. *Manic depressive insanity* (manic stage), 46. *Typhoid fever*, 39-34. In the latter case, the number was the same at a higher level.

Observations in some other conditions were: *Carcinoma of colon*, 48; *carcinoma of stomach*, 52; *acute pleurisy*, 52; *pharyngeal abscess*, 52; *frontal sinusitis*, 55; *abortion*, 46; *hemorrhagic septicemia*, 28; and in 2 children, *ileocolitis with convulsions*, 36; *encephalitis*, 44.

In successive determinations, there was apparently no relation between the prognosis and the increase or decrease in the alkali reserve of the spinal fluid. The reaction often differed in fluids a few cubic centimeters removed from each other, and the alkali reserve varied as much as 14 points in 5 cc fractions. The range of maximum variations in various fractions was from 0 to 24 volumes per cent. Some cases were mentally clear with variations as much as 14 volumes per cent (F 8215, C. S., lues, 14 volumes per cent; F 8885, C. S., lues, 6), whereas others were hazy, or comatose with variations from 0 to 24 (F 8637, typhoid, 0; F 8823, tuberculous meningitis, 2; F 8853, encephalitis lethargica, 5-1; F 9151, uremia, 14; F 9470, cerebral hemorrhage, 24; F 9732, skull fracture, 6; F 9918, miliary tuberculosis, 0; G 2896, miliary tuberculosis, 10; G 3031, miliary tuberculosis, 4-6).

The foregoing data show that the alkali reserve (carbon-dioxide combining power) of the cerebrospinal fluid may vary at different levels, and the hydrogen-ion concentration may differ. The processes, both mechanical and electrical, which would tend to bring about chemical equilibrium, may have some effect upon the clinical state of the person, but so far no correlation can be made. The circulation must be comparatively slow, and no real comparison with other factors can be made unless fluids from all levels, especially around the brain (ventricles) itself, can be studied. The data show no correlation between the plasma-alkali reserve and that of the fluid from a given level. This is probably because the proper venous blood cannot be selected—the difference in composition, in this respect, between the blood from an arm vein and that in the vertebral canal veins may be marked. McClendon<sup>1</sup> noted the alkali reserve to be about 10 per cent lower in the spinal fluid than in the plasma, the alkali reserve, CO<sub>2</sub> tension and hydrogen-ion concentration of blood plasma and spinal fluid in the same person being otherwise the same. Meier<sup>2</sup> considered the CO<sub>2</sub> tension the same or somewhat lower than in the blood. The CO<sub>2</sub> capacity curve was smaller and less buffered than in the serum. *Tabes* and tuberculous meningitis had no effect upon the reaction or CO<sub>2</sub> capacity. The reserve was decreased in 1 case of epidemic meningitis. Tashiro and Levinson<sup>3</sup> suggest the presence of another acid besides carbonic in epidemic meningitis, while carbonic is the acid in tuberculous meningitis. Egerer-Seham and



Nixon<sup>4</sup> reported an average of 53.1 for normals (range, 46.5 to 61.7), decreased in narcolepsy (28.15), pyelonephrosis (23.75), diabetes (22.28) and acidosis (13.6). Tokuoaka and Ogasawara<sup>5</sup> noted 63 volumes per cent for spinal fluid in healthy women, with 54.4 volumes per cent for the blood. They noted a decrease after starvation, and in cancer (3 volumes per cent less in spinal fluid and 4.7 volumes per cent less in the blood). Macleod<sup>6</sup> states that "There is as large a percentage of bicarbonate in the cerebrospinal fluid as in the blood plasma. The so-called alkaline reserve, as determined by the Van Slyke method is, therefore, the same as in blood plasma (viz, about 50)."

Nagasawa<sup>7</sup> reports that the combined  $\text{H}_2\text{CO}_3$  increases with the severity of the symptoms in epidemic meningitis, associated with the increase in polymorphonuclear cells. Bacterial growth increased the combined carbon dioxide, irrespective of that of the blood. Collip and Backus<sup>8</sup> considered that the  $\text{CO}_2$  combining power of the plasma is an approximate index of the alkali reserve of the body fluids. The present results, however, suggest that this does not hold under all conditions. In all their human cases, the plasma alkali reserve was higher than that of the spinal fluid.

The variations in composition of the cerebrospinal fluid at different levels has been noted by various workers. Weigeldt<sup>9</sup> and others noted the variation in cell count at different levels, and Ayer and Foster<sup>10</sup> noted the diagnostic significance of differences in the protein content of cistern and lumbar sac fluid. The present work points out that besides the variation in cell count there may also be a variation in reaction and alkali reserve at different levels.

In the data given the curves of distribution of the frequency of cases when plotted in graphic form show a gross similarity between those with no central nervous system symptoms, those with normal globulin and those with normal pressure. The pathological conditions show greater limits of dispersion than the normals. The greatest frequency of the normals lies between 50 and 58 (52 to 54), while in the pathological conditions, the number lies between 40 and 50 (46) for the lowest fraction of the fluid.

**Summary and Conclusion.** 1. There is no direct correspondence between the carbon-dioxide combining power of the cerebrospinal fluid and the type of disease.

2. A difference in  $\text{CO}_2$  combining power was noted in many fluids at different levels around the brain and cord, variations being from 0 to 24 volumes per cent.

3. The average carbon-dioxide combining power of the spinal fluid (lowest fraction) in the absence of nervous symptoms was 50.7 volumes per cent, and was about the same as the average of that of the venous blood taken from the arm, although this was not necessarily true of the individual case.

4. This ratio varied greatly in the presence of symptoms rather

than in diseases as a whole, the spinal fluid number being equal, greater or less than the blood plasma.

5. The average carbon-dioxide combining power of the spinal fluid (lowest fraction) for patients with headaches, was 38.9; unconscious patients, 39.5; stuporous, semicomatose, hazy, drowsy, 41.58; delirium, mania, 41.66; convulsions, 43.37. The ranges for these symptoms, however, covered wide limits.

6. Average for negative Wassermann spinal fluids (lowest fraction), 49.1 volumes per cent; positive Wassermann spinal fluids (lowest fraction), 44.3 volumes per cent.

7. Average for negative globulin (lowest fraction), 45.87 volumes per cent; positive globulin, (lowest fraction), 41.14 volumes per cent.

8. Average for normal pressure (lowest fraction), 49.36 volumes per cent; increased pressure (lowest fraction), 42 volumes per cent.

9. Average for normal cell count (lowest fraction), 48.5 volumes per cent; 8 (and above) cells (lowest fraction), 43.1 volumes per cent.

10. A difference in reaction was noted at different levels.

11. No parallelism was noted between the reaction of the fluid and the alkali reserve.

12. There appeared to be no relation between increase or decrease in the alkali reserve as the case progressed and the prognosis.

13. The carbon-dioxide combining power varied within greater limits in the pathological than in the normal conditions.

14. The greatest frequency of the normal conditions was between 50 and 58 (52 to 54), and in the pathological conditions between 40 and 50 (46) for the lowest fraction.

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## BUFFER SOLUTIONS IN INTESTINAL DISEASES.

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FECES from a healthy person on a properly balanced diet should be either neutral, slightly alkaline or slightly acid in reaction. When carbohydrates are taken in excess, acidity is the rule. If the protein intake is excessive, the stool is likely to be alkaline.

Various pathological conditions and bacterial infections influence the reaction of the feces. Infection with *Bacillus fecalis alkaligenes* gives rise to a decidedly alkaline reaction. Infection with *Bacillus aërogenes capsulatus*, or with Gram-positive, single or double cocci, frequently produces a highly acid stool.

In chronic excessive saccharobutyric infections in babies, the buttocks and anus frequently become highly irritated as a result of the acid movements. While on the Boston Floating Hospital a number of years ago, one of us (Eberhard) watched with Dr. Arthur I. Kendall many cases of *Bacillus aërogenes capsulatus* infection, in which the buttocks of the babies were so severely excoriated as a result of the marked fecal acidity that mothers made more comment about the skin condition than the diarrhea.

The gastroenterologist learns by experience that chronic saccharobutyric infections are decidedly more common than the average internist realizes. These infections often mimic such conditions as gastric and duodenal ulcers, gall-bladder diseases, etc., so that operations have been performed in error. Too much credit cannot be given to Herter, Bassler and Kendall for their painstaking researches in intestinal bacteriology and the clinical interpretation of the infections.

The purpose of this paper, is not to give a detailed description of chronic saccharobutyric infection and its treatment, but to report concerning the use of buffer solutions in overcoming the high acidity which is incident to the infection. However, a brief summary of the symptoms and laboratory findings may be helpful. The condition is most frequently caused by *Bacillus aërogenes capsulatus*, also known as the gas bacillus or Welch bacillus. This is a Gram-positive spore-former, normally present in the intestine in small numbers; it produces gas and gives rise to a marked odor of butyric acid when sown in sterile milk. This odor of rancid butter is characteristic of the feces of patients with this infection. The cultures from the feces may also reveal the presence of *Bacillus putrificus*, the bacillus of malignant edema, and Gram-positive

coccal forms. One of the characteristics of the feces, directly examined on a slide, is the marked preponderance of all Gram-positive organisms. Among the symptoms is diarrhea preceded by a crampy pain in the abdomen; it alternates with periods of normal defecation. During these periods the symptoms may be simply marked or slight crampy pains throughout the abdomen. This pain, like the diarrhea, is made worse by sugars; in fact, by all carbohydrates. Unlike gastric ulcer, neither food nor alkali affords relief. A brisk purge relieves the diarrhea and the pain for only a short time. The feces are characteristic; they have a very light yellow color, doubtless due to the presence of a large amount of hydrogen in the bowel and its reducing action on the bile pigments. Patients frequently comment on the marked odor of rancid butter, due to the presence of butyric acid. The feces usually are markedly acid on account of the presence of propionic, butyric, valeric and caproic acids. Macroscopically, they are foamy and contain much mucus; occasionally blood is visible; a low specific gravity is common. Much gas is formed, as a rule, when the feces are incubated in Bauermeister or other fermentation tubes. Microscopically, many degenerated cells are found, perhaps as a result of the irritant action of certain products of the fermentation. Aphthae in the mouth are common, especially after partaking of sweets such as candy and ice-cream. One of us (Eberhard), has frequently found traces of occult blood in the gastric contents and feces of these patients; this lends support to the theory that such infection might be the cause of ulcers in the alimentary canal. Neurasthenic symptoms are common, anxiety, depression, etc. Belching of gas and acid risings are also common due, no doubt, to an increased gradient in the ileum and the upper colon. The treatment, generally, is a high protein diet for a time, not continued too long, however, since the organisms early become facultative. Others forms of treatment are transintestinal lavage with hypertonic salt solution, rectal implantation of *Bacillus coli*, cultured from the patient's own feces, irrigation with alkalies, etc.

While treating patients with such infection they too often become restive on account of frequent relapses. Even with the best forms of treatment, recurrences in the face of progress are common. Patients are annoyed with the pain and excoriation of the buttocks and demand some form of relief. Most clinicians prescribe colon irrigation of sodium bicarbonate which at least gives some comfort for a while. At times, however, the carbon dioxide gas generated from the bicarbonate is more annoying than the pain and diarrhea.

We have noted one alarming case of cardiac embarrassment due to the gas. Moreover, the sudden generation of gas may cause a rupture of an ulcerated bowel.

In order to neutralize the intestinal contents, without the pro-

duction of gas, we have applied buffer solutions in the treatment of these infections. The solutions are administered by rectal injection. The results have been extremely encouraging, as may be seen from the typical cases reported below.

Clark<sup>1</sup> defines a buffer solution as a solution which is able to resist change in its hydrogen-ion concentration by addition or loss of acid or alkali. Such solutions usually contain two compounds. Take, for instance, a solution containing both a primary and a secondary phosphate: Such a solution can combine with fairly large amounts of either acid or alkali. Acids cannot impart to it a reaction more acid than that of phosphoric acid until all the phosphates have been decomposed. Alkalies cannot impart to it a reaction more alkaline than that of trisodium phosphate until all the phosphates have been converted into that salt.

In the treatment of intestinal acidity, it has been necessary to use buffer solutions which could not possibly liberate gases within the intestine, while neutralizing its acid contents; therefore, bicarbonates could not be used. Recourse has been had to two buffer solutions, which may be designated as the phosphate buffer solution and the citrate buffer solution. Both solutions were made according to the directions of Sørensen<sup>2</sup> immediately prior to use. If the solutions be kept for some time, they may become infected by moulds; this is especially true of the citrate buffer solution.

The phosphate buffer solution had a hydrogen-ion concentration  $P_H$  of 8.043; it was prepared by mixing a  $\frac{1}{15}$  molar solution of primary potassium phosphate and a  $\frac{1}{15}$  molar solution of secondary sodium phosphate in the ratio of 0.5 mil of the former to 9.5 mils of the latter.

The citrate buffer solution had a hydrogen-ion concentration  $P_H$  of 12.364; it was prepared by mixing a  $\frac{1}{10}$  molar solution of secondary sodium citrate, and an exactly  $\frac{1}{10}$  normal solution of carbonate-free sodium hydroxide in the ratio of 4 mils of the former to 6 mils of the latter.

Of the two buffers, the citrate solution was used more frequently, since it possessed a greater alkali reserve; that is, had a lower hydrogen-ion concentration and a higher hydroxyl-ion concentration, and, therefore, was able to neutralize more acid before its reaction was reduced to that of normal feces which have a hydrogen-ion concentration  $P_H$  between 7.0 and 7.5 according to Robinson.<sup>3</sup>

A résumé is given of three typical cases:

CASE I.—Mr. A. Enterocolitis for ten years. Six to eight movements daily of a very light yellow stool. Marked tenesmus. Great amount of flatus. Eczema of anus and buttocks. Frequent attacks of colic, followed by diarrhea. Gastric analysis showed a marked hypersecretion of the fasting stomach, (120 mils); free hydrochloric acid, 60; total acidity, 80. A fractional test breakfast

of 250 mls of tea and 50 grams of bread showed the highest peak of free hydrochloric acid at the second hour. Motor end point at three hours. Roentgen ray revealed a normal stomach, with atony. Feces: Excessively acid, great excess of all Gram-positive organisms; culture yielded *Bacillus aërogenes capsulatus* and many single and double cocci. Gas unusually abundant in Bauermeister fermentation tube. After diet and other treatment failed to reduce the acidity and diarrhea, 1 liter of the phosphate buffer solution was injected per rectum. The next movement was neutral in reaction, the number of movements never exceeded two daily. Above all, the colic, which had persisted for years, was relieved. Frequent injections of the buffer solution controlled the remaining symptoms. The eczema disappeared in a surprisingly short period of time.

CASE II.—Mrs. C., aged thirty years. For two years has had "sore tongue," an examination of which showed marked redness of the dorsum and two small ulcers on the tip. Patient states the condition disappears for a week, or more, then returns. At times, small ulcers also develop near the frenum of the tongue. No gastrointestinal symptoms, excepting a persistent pain in the epigastrium; not relieved by food, alkali nor lavage. Wassermann reaction negative with both blood and spinal fluid. Roentgen ray examination of gastrointestinal canal, negative. Gastric analysis: 110 mls of gastric contents after a twelve-hour fast; fractional analysis showed decided hyperacidity; highest peak at one hour after tea and toast; motor end point at two and one-half hours. Feces: Marked preponderance of all Gram-positive organisms. After a Bassler modification of the Schmidt and Strassburger test diet, light yellow feces with a marked acid reaction and a pronounced odor of butyric acid, containing reduced bile pigments, according to the mercuric chloride (sublimite) test, and showing a decided increase of all Gram-positive organisms; no occult blood; excessive gas on incubation in Bauermeister tubes. Treatment: High protein diet, transintestinal lavage, etc., gave no relief; the ulcers near the frenum and the soreness of the tongue continued; the stool remained markedly acid in reaction. Two high colon injections of the citrate buffer solution produced an alkaline stool with no return of the tongue or mouth condition.

CASE III.—Male, aged forty years. History of persistent general abdominal pain for ten years. Five years ago had appendix removed and gall-bladder drained for three weeks by cholecystotomy; much improvement was experienced for three months, then the general indefinite pain returned. Examination showed a well-nourished man; teeth and tonsils in good condition; chest negative; maximum systolic pressure, 128/82; reflexes normal;

abdominal habitus normal; many diffuse tender points, especially along the colon. Sigmoidoscope examination of the rectum showed marked general inflammation with tendency toward spasm. Gastric analysis revealed 120 mls of contents in the fasting stomach. Free hydrochloric acid was 62; total acidity, 96. An Ewald test breakfast of 250 mls plain tea and 50 grams toast showed the motor end point at three and one-half hours. The highest values for both free hydrochloric acid and total acidity occurred at two hours. Occult blood was absent. A culture was made of the contents of the fasting duodenum including bile, obtained after the administration of a 25 per cent solution of magnesium sulphate; *Bacillus coli* was found in the culture. Feces: Were strongly acid, contained much adherent mucus and had a decided odor of butyric acid; fatty acids were extremely abundant. *Bacillus aërogenes capsulatus* and many single cocci preponderated in the bacterial flora. A count showed 86 Gram-positive to 14 Gram-negative organisms. In fermentation tubes, gas and acid were formed in excessive amounts. The patient had a diarrhea, five or six movements daily, very acrid, and causing much tenesmus. Colic was so severe that morphine had to be given from time to time. A small amount of food produced immediate distress, and retention vomiting was common. A Roentgen ray study revealed only a mild pylorospasm. The patient had been advised to have another operation.

Duodenal lavage twice weekly with drainage of the bile tracts by administration of a 25 per cent solution of magnesium sulphate, rest in bed, *Bacillus coli* vaccine and a high protein diet relieved all the symptoms but the acid stool and tenesmus. These symptoms were relieved by three treatments with the citrate buffer solution at semiweekly intervals, administering 1 liter of the solution by rectum at each treatment. One month after the last injection of buffer solution, the gastric motility was normal, and the ratio of Gram-positive to Gram-negative organisms was 40:60. The drainage of bile, high protein diet, and vaccine reduced the colon gradient and relieved the pylorospasm, while the buffer solution relieved the acid stool and tenesmus. This patient will probably require a number of injections of the buffer solution, and will have to maintain a high protein intake in order to keep in control the Gram-negative organisms. The buffer solution can at least be depended upon for relief.

These cases are examples of what has been accomplished by rectal injection of buffer solutions. Many cases have been treated; and a number are still under observation. While we do not claim curative results nor anything revolutionary, yet, we think that buffer solutions are worthy of trial for the relief of distressing colic and for the securing of bowel neutrality.

**Summary.** Clinically, we have noted a marked improvement in subjective and objective symptoms of intestinal disease with the use of buffers. The ratio between Gram-negative and Gram-positive organisms was reestablished very frequently after the first or second enema. We feel that while the use of a buffer solution is still experimental, enough evidence has been gathered to indicate its use and to show its value.

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**CREATININEMIA: BASED UPON A STUDY OF FIFTEEN HUNDRED BLOOD CHEMICAL ANALYSES.**

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THE introduction of clinical methods for blood chemical analyses gave a great impetus to the study of the nephropathies. So great is the reliance placed upon these findings that a blood chemistry examination is commonly demanded in every case of renal disease. Diagnosis, prognosis and treatment are influenced to a considerable degree by the results of these tests.

The significance of the retention of non-protein nitrogen and of its principal components, urea, uric acid and creatinin, has many times been clearly stated. However, a review of the literature discloses the fact that, in the case of creatinin, the conclusions, considering their importance, have been based upon rather small groups of cases. In respect to creatinin, attention has so largely been focussed upon its retention in nephritis that it appeared desirable to study a large consecutive series in order to ascertain whether that condition may be present in other states. The almost routine use of blood chemical analyses on the Medical Service of the Long Island College Hospital offered an excellent opportunity for collecting and analyzing such a group. It was felt that the analysis of these 1500 cases, while, perhaps, not modifying conclusions already reached, would be of value by adding such confirmation to present views as only a large series can give.



TABLE I.

Case.	Age.	Sex.	Blood chemistry.					Date of discharge or death.	Result.	Diagnosis.	Complications and remarks.
			No. of days before death.	Date.	Creati- nin.	Urea N.	Uric acid.	Sugar.			
1. A. G.	46	F.	6	May 17, 1920	20.0	300.0	10.00	196.0	Died	Chronic glomerulonephritis	Semicomatose and delirious.
2. J. S.	33	F.	1	22, 1920	30.0	300.0	50.00	285.0	Died	Chronic glomerulonephritis	Uremia.
3. M. V.	24	M.	6	April 1, 1920	28.0	300.0	50.00	240.8	Died	Acute diffuse glomerulonephritis	Uremia.
4. E. C.	75	F.	1	June 6, 1920	15.0	200.0	20.00	181.8	Died	Chronic glomerulonephritis	Uremia.
5. V. H.	25	M.	0	June 13, 1920	20.0	300.0	15.50	235.2	Died	Chronic glomerulonephritis	Uremia.
			11	Feb. 17, 1920	7.5	50.0	6.20	333.3	Died	Acute exacerbation of chronic glomerulonephritis	Uremia.
			7	21, 1920	8.6	300.0	12.50	200.0			
			4	24, 1920	15.0	300.0	8.20	143.0			
6. C. J.	39	M.	1	27, 1920	20.0	375.0	5.00	138.0			
			0	June 22, 1920	15.0	375.0	35.70	86.0	Died	Chronic glomerulonephritis	Uremia, pulmonary tuberculosis, amyloid kidneys and spleen; necropsy showed pulmonary tuberculosis amyloid kidneys and spleen. Uremia.
7. W. D.	27	M.	7	May 28, 1920	15.0	130.4	8.80	200.0	Died	Chronic glomerulonephritis	Uremia; diagnosis confirmed at necropsy.
8. R. M.	25	M.	3	June 1, 1920	15.0	50.0	33.30	153.8	Died	Chronic glomerulonephritis	Uremia.
			0	Feb. 20, 1921	15.0	150.0	10.00	142.0	Died	Chronic glomerulonephritis	Uremia.
9. J. S.	28	M.	10	Oct. 27, 1921	15.0	60.0	6.25	181.0	Died	Chronic glomerulonephritis	Uremia.
10. A. C.	25	F.	5	Nov. 1, 1921	14.0	75.0	10.25	136.0	Died	Chronic glomerulonephritis	Uremia.
			5	May 4, 1919	8.0	117.6	...	143.0	Died	Bichloride poisoning nephrosis with anuria	Took three bichloride tablets, April 28, 1919; necropsy showed coagulation necrosis of kidneys and ulcers in stomach. Uremia.
			3	5, 1919	10.2	86.8	...	166.6	Died		
			1	7, 1919	13.3	140.0	14.12	250.0	Died		
11. T. R.	41	M.	1	Jan. 23, 1920	11.0	300.0	25.00	70.0	Died	Chronic glomerulonephritis	Uremia.
12. R. V.	23	F.	17	Oct. 20, 1919	6.7	60.0	11.10	80.0	Died	Nephrectomy, other kidney being congenitally cystic	Pleurisy and pericarditis.
13. C. K.	66	M.	13	Nov. 4, 1920	10.3	100.0	16.00	110.0	Died	Chronic glomerulonephritis	Uremia; confirmed by necropsy
14. A. C.	29	M.	3	Aug. 4, 1921	10.0	225.0	16.25	125.0	Died	Chronic glomerulonephritis	Lobar pneumonia; confirmed by necropsy.
15. J. C.	28	M.	10	Dec. 24, 1918	3.2	22.40	...	80.0	Died	Acute diffuse glomerulonephritis	Phenolsulphonphthalein test; 0.
16. E. C.	35	F.	3	Nov. 11, 1921	8.8	26.60	6.66	153.0	Died	Chronic glomerulonephritis	Anuria; uremia.
17. A. A.	29	F.	6	Feb. 17, 1920	6.5	100.0	10.00	142.8	Died	Bichloride poisoning; nephrosis (coagulation necrosis tubules)	Uremia; perforation of uterus, peritonitis and bacteremia.
			5	18, 1920	7.5	200.0	...	...	Died		Tertiary syphilis; confirmed by necropsy.
			4	19, 1920	6.6	115.3	6.30	200.0	Died	Chronic glomerulonephritis	Uremia; confirmed by necropsy.
18. G. N.	21	F.	3	Nov. 11, 1919	7.3	230.0	12.50	200.0	Died	Chronic glomerulonephritis	General paresis; uremia.
19. L. K.	34	F.	2	Mar. 12, 1921	6.00	100.0	25.00	95.0	Died	Chronic glomerulonephritis	Cardiac incompetence; limited fluid intake and digitalis yielded marked improvement.
20. S. L.	55	F.	0	Sept. 14, 1921	6.75	125.0	25.00	111.0	Died	Chronic glomerulonephritis	
21. W. G.	53	M.	0	Oct. 27, 1919	6.75	150.0	25.00	105.0	Died	Chronic glomerulonephritis	
			7	Oct. 27, 1919	6.50	88.2	5.00	133.3	Died	Chronic glomerulonephritis	
			3	Aug. 10, 1920	5.00	150.0	5.50	119.0	Died	Mixed type, chronic glomerulonephritis plus nephrosis	
22. M. C.	48	M.	...	Aug. 14, 1920	6.00	75.0	5.00	91.0	Im-		
			...	25, 1920	6.00	75.0	12.50	91.0	proved		
			...	Sept. 2, 1920	4.00	60.0	4.20	133.0			
			...		3.00	37.5	...	...			

23. A. L.	57	M.	Aug. 28, 1920	10	2.25	150.0	7.10	250.0	Sept. 7, 1920	Died	Chronic glomerulonephritis	Uremia.
24. R. M.	24	M.	Sept. 4, 1920	3	6.00	360.0	10.00	285.0	Aug. 12, 1921	Died	Chronic glomerulonephritis	Arteriosclerosis; uremic.
25. D. S.	43	M.	Oct. 18, 1920	398	5.00	100.0	10.00	166.0	Nov. 24, 1921	Died	Chronic glomerulonephritis	Confirmed by necropsy.
26. S. W.	46	F.	Oct. 22, 1920	294	2.84	37.5	7.13	83.0	Nov. 24, 1921	Died	Chronic glomerulonephritis	Cerebral hemorrhage; myocardial insufficiency; twice discharged in improved condition; died a cardiac death.
27. H. G.	43	F.	Oct. 27, 1921	28	2.16	55.0	9.17	71.0	April 12, 1921	Died	Chronic glomerulonephritis	Confirmed by necropsy.
28. M. A.	21	F.	Nov. 1, 1921	23	5.80	48.5	12.50	133.0	Mar. 30, 1920	Died	Chronic glomerulonephritis	Albuminuric retinitis; phenol-sulphonethalein test, 20 per cent.
29. B. R.	35	M.	Nov. 11, 1921	13	5.00	60.0	14.40	111.0	Aug. 13, 1921	Im-proved	Chronic glomerulonephritis	Lead poisoning.
30. J. M.	47	M.	Oct. 20, 1920	6	5.00	33.8	10.00	100.0	Jan. 28, 1920	Died	Chronic glomerulonephritis	Uremia.
31. H. W.	43	M.	Nov. 10, 1920	169	2.00	18.8	5.55	118.0	April 4, 1921	Died	Chronic glomerulonephritis	Uremia; died in coma; aortic regurgitation; confirmed by necropsy.
32. S. C.	43	F.	Nov. 25, 1920	153	3.75	18.8	7.13	111.0	July 7, 1919	Died	Chronic glomerulonephritis	Myocardial insufficiency.
33. A. C.	60	M.	Dec. 22, 1920	141	2.13	16.7	5.55	111.0	Aug. 20, 1919	Died	Chronic glomerulonephritis	Arteriosclerosis; cerebral angio-spasm.
34. H. L.	66	M.	Jan. 6, 1921	96	1.36	30.0	3.13	125.0	April 8, 1919	Im-proved	Chronic glomerulonephritis	No glycosuria.
35. R. F.	32	F.	Mar. 15, 1921	28	1.50	42.8	3.70	153.0	Nov. 25, 1921	Died	Chronic glomerulonephritis	Syphilis; date of death unknown.
36. M. S.	18	F.	Mar. 22, 1921	12	2.13	24.9	4.15	400.0	Sept. 9, 1920	Died	Chronic glomerulonephritis	Syphilis; date of death unknown.
37. C. M.	67	F.	Apr. 6, 1921	0	3.33	100.0	16.25	133.0	July 30, 1920	Died	Chronic glomerulonephritis	Chronic myocarditis; date of death unknown.
38. A. B.	58	M.	Mar. 21, 1919	108	3.17	22.4	...	...	June 15, 1920	Died	Chronic glomerulonephritis	Myocardial insufficiency; died of bronchopneumonia.
39. F. N.	34	M.	Apr. 5, 1919	146	3.12	16.66	...	...	May 29, 1919	Died	Chronic glomerulonephritis	Tertiary syphilis; died of bacteremia.
40. H. W.	63	M.	Mar. 27, 1919	...	3.07	19.6	...	...	April 19, 1921	Died	Chronic glomerulonephritis	Prostatic hypertrophy.
41. W. N.	75	M.	Oct. 7, 1921	49	3.00	17.6	5.20	267.5	Mar. 29, 1919	Im-proved	Chronic glomerulonephritis	Arteriosclerosis; emphysema; alive May 22, 1922, but unable to work.
42. C. S.	40	M.	May 3, 1920	?	2.00	20.0	4.20	105.0	Jan. 28, 1919	Im-proved	Chronic glomerulonephritis	Returned to work.
43. R. H.	42	M.	July 10, 1920	?	1.90	19.0	2.00	116.0	Oct. 28, 1919	Im-proved	Chronic glomerulonephritis	
			Aug. 8, 1920	?	1.50	25.0	...	57.0				
			Aug. 13, 1920	?	3.00	60.0	10.00	100.0				
			July 13, 1920	?	3.00	30.0	10.00	143.0				
			June 8, 1920	7	1.50	16.0	3.40	133.3				
			May 12, 1919	7	2.86	39.2	5.04	116.2				
			Apr. 9, 1920	10	2.72	91.6	16.25	...				
			Mar. 19, 1919	...	2.70	33.6	...	...				
			Jan. 14, 1919	...	2.60	16.8	...	...				
			Sept. 29, 1919	...	2.60	50.0	...	...				
			Oct. 8, 1919	...	2.50	60.0	4.50	...				

**LITERATURE.** The pioneer work upon creatinin retention was done by Folin and Denis.<sup>1</sup> There had been but few previous determinations of this substance in the blood. Earlier researches had centered around the estimation of creatinin in the urine. Because of its uniform rate of elimination, even on a low-protein diet, and of its relation to creatin, it furnished a valuable index to the level of tissue metabolism. Hence, as might be expected, the elimination of creatinin in the urine was found to be increased in febrile states and in exophthalmic goiter.

Physiological data upon creatinin and its role in the metabolic processes foreshadowed its eventual clinical importance. Of all the non-protein nitrogenous products it is the one least influenced by dietary factors. It is believed to be derived exclusively from the creatin contained in all tissues, of which substance it is the anhydrid. Placing an individual upon a meat-free diet does not materially diminish the creatinin excretion. However, the ingestion of large doses (20 gm.) of creatinin had been shown by Rose and Dimmitt<sup>2</sup> to lead to a perceptible increase (0.49 gm.) in the output of creatinin.

Because of the fact that the kidneys eliminate creatinin with especial ease, its blood concentration (1 to 2 mg. per 100 cc) remains remarkably constant. This fact suggested the employment of a clinical method for the determination of the blood creatinin.

Folin and Denis<sup>1</sup> measured the creatinin in the blood of 200 hospital patients with non-renal conditions and found no retention in them. On the other hand, accumulation of creatinin was noted in uremia and terminal nephritis, and high figures appeared to portend early death.

Myers and Lough<sup>3</sup> confirmed these findings. Their conclusions were that a creatinin figure of from 2.5 to 3 is suspicious; that a reading of from 3 to 5 indicates severe renal damage and that figures over 5 foreshadow a fatal termination within two months.

In 1916, Chace and Myers<sup>4</sup> formulated their views upon the clinical importance of creatinin in the following words: "As a prognostic test the blood creatinin has been found of very great service, over 5 mg. to 100 cc having invariably proved fatal after the lapse of a comparatively short period of time. During the terminal stages of the disease, the concentration of the creatinin gradually rises, reaching 15 to 30 mg. in most cases at death."

In 1918, Myers and Killian<sup>5</sup> reaffirmed the same views.

For a time, serious doubt was cast upon the whole question of creatininemia, when McCrudden and Sargent,<sup>6</sup> in 1916, announced that all of the variations in the colorimetric readings could be accounted for by slight differences in the amount of picric acid contained in the solution. They stated that the color due to the creatinin contributed but a small portion of the total hue. As the Folin colorimetric method had been the one employed in the

clinical determinations, this indictment, if true, would have completely nullified all previous work on creatinin retention. Folin and Doisy<sup>7</sup> immediately reinvestigated the whole subject. Together with McCrudden and Sargent, they examined the latters' picric acid and found it to be surprisingly impure. Pure picric acid gives only a faint tinge to the solution.

Since that time the literature upon the subject has not been voluminous, and there has been no serious contradiction to the conception originally promulgated by Folin and Denis. Rabino-witch,<sup>8</sup> in 1921, emphasized the prognostic value, reporting 14 cases with creatinin figures over 5, all of which were necropsied and showed marked renal damage.

The general rule that laboratory findings must be correlated with the clinical data in order to be properly interpreted allows no exception in the case of creatinin. If the retention be of sudden onset and due to a remediable cause, such as ureteral calculus or hypertrophied prostate, prompt recovery may be expected upon removal of the defect. This fact is brilliantly illustrated by the experiments of Keith and Pulford.<sup>9</sup> These investigators produced hydronephrosis in dogs by ligating the ureters with a rubber band. When the obstruction was maintained for too long a time, permanent kidney damage was done and the animals died; but when the obstruction was removed in time, even though the blood creatinin had already reached abnormally high values, complete recovery took place.

**TECHNIC.** The technic originally described by Folin and Denis still occupies first place. Modifications subsequently suggested have added nothing to it. It was the method employed in this series of blood analyses. The details of the test are contained in an article by Folin and Wu.<sup>10</sup>

**MATERIAL STUDIED.** Out of 1500 routine blood chemical analyses taken in the wards of the Long Island College Hospital, there were selected all of those cases, regardless of diagnosis, which exhibited a blood creatinin figure in excess of 2.5 mg. per 100 cc. The routine use of these analyses should be stressed. Only a small percentage of the whole group of individuals was suffering from renal disease. The data upon all of the creatininemic patients are tabulated in Table I. The relation between the date of the blood chemical analysis and that of death should be particularly noted, inasmuch as the creatinin determination is so commonly used as a prognostic guide. The patients showing retention were followed up after their discharge from the hospital, and every effort was made to determine the exact date of death.

*Analysis of Table I.* Forty-three cases showed at some period a blood creatinin value in excess of 2.5. Table II, below, shows that every one of these patients gave evidence of renal damage.

TABLE II.—SUMMARY OF CLINICAL DIAGNOSES IN ALL CASES  
SHOWING CREATININEMIA.

Chronic diffuse glomerulonephritis . . . . .	35
Acute exacerbation of chronic glomerulonephritis . . . . .	2
Acute diffuse glomerulonephritis . . . . .	2
Bichloride poisoning, nephrosis with anuria . . . . .	2
Mixed type, chronic glomerulonephritis plus nephrosis . . . . .	1
Nephrectomy, other kidney being congenitally cystic . . . . .	1

These findings are quite in accord with the accepted view. It may, perhaps, appear surprising not to find a single borderline or non-nephritic case out of such a large series. The deduction is safe that creatinin is very easily eliminated by the normal or even the moderately damaged kidney and that creatinin retention is an unmistakable sign of great functional inefficiency. However, it must be borne in mind that anuria, from any cause, whatsoever, is capable of causing a rapidly mounting creatininemia. Reference to Case X, in which there was complete anuria, due to bichloride poisoning, demonstrates how quickly creatinin retention figures may rise in the absence of urinary secretion. It is noteworthy that all of the patients in the retention category, with the exception of the three anuric individuals, gave evidence of lesions of the glomeruli.

PROGNOSTIC INFERENCES. The first 14 cases listed in Table I attained creatinin figures of 10 mg. per 100 cc or more. All of these patients died within less than three weeks. The longest period of survival was seventeen days. The average length of life after reaching this figure was four days.

Fifteen patients yielded readings between 5 and 10 mg. per 100 cc. Eleven of these individuals died uremic within seventeen days, the average being six days. Three others have since died at intervals of two hundred and ninety-eight, one hundred and seventy-four and forty-nine days respectively. Two cases of this group, Nos. XXII and XXVI, deserve especial consideration, as they indicate that recovery may take place even after the creatinin figure has exceeded 5. The former exhibited the block type of retention. The patient was edematous and oliguric, and there was myocardial insufficiency. Treatment with rest, limitation of fluid intake and digitalis resulted in marked improvement with a parallel reduction in the retention figures. He was discharged greatly improved at the end of a month. Case XXVI actually attained normal blood chemical values and was discharged from the hospital in excellent condition. A concurrent cerebral hemorrhage with cardiac decompensation subsequently caused death, but at that time there was but slight retention of creatinin and urea. These 2 cases serve to emphasize the fact that with retention exceeding 5 mg. per 100 cc, the prognosis as regards the renal condition, while grave, is not necessarily hopeless.

TABLE III.—OUTCOME WITH VARIOUS DEGREES OF RETENTION.

Creatinin figure.	Died.	Max. No. of days.	Aver. No. of days.	Unimproved.	Improved.
Over 10 mg. . . .	14	17	4	0	0
5.0 to 10 " . . .	14	298	42	0	1
2.5 to 5 " . . .	16	..	..	0	5

COMPARISON WITH RETENTION OF UREA AND URIC ACID. It will be observed that the figures for creatinin and for urea appear to rise in a rough ratio; but too much reliance must not be placed upon this relationship. Thus one analysis yielded a reading of 6 mg. of creatinin and 300 mg. of urea nitrogen. In another case, values of 8.8 mg. of creatinin and only 26.6 mg. of urea nitrogen were obtained. There was not a single instance in which creatinin but not urea was retained. In a previous paper upon uremia,<sup>11</sup> studied from the aspect of retention of urea, the fact was pointed out that urea nitrogen furnishes a more delicate guide and gives earlier evidence of renal deficit. In that group of 29 cases, the rough ratio between creatinin and urea nitrogen was likewise apparent.

Accumulation of uric acid bears a very inconstant relation and its readings are of little assistance in forming a prognosis. Together with the other non-protein nitrogen ingredients, its blood values are increased in nephritis, but the figures are so variable that sound inferences cannot be drawn from the level of its retention. Myers, Fine and Lough<sup>12</sup> expressed the belief that uric acid, because of the complexity of its molecule, is eliminated with great difficulty and that, consequently, retention of this substance is an indication of early nephritis. The author<sup>13</sup> has just completed the study of a series of cases with retention of uric acid but of none of the other non-protein nitrogen substances. So far as he has been able to observe, this retention occurs in a great variety of unrelated conditions and is not a reliable index to incipient renal insufficiency.

**Summary.** Fifteen hundred blood chemical analyses were made upon patients in the wards of the Long Island College Hospital. As it was desired to study creatinin retention in any conditions in which it might possibly occur, there was no selection of cases. The blood values exceeded 2.5 mg. per 100 cc in 43 patients. An analysis of this group showed that in all there were other unmistakable evidences of renal deficit. Forty cases were diagnosed as glomerulonephritis, while the other 3 patients were anuric.

Fourteen patients attained figures of 10 mg. or over per 100 cc. All of these patients died within seventeen days, the average length of life being four days. Of 15 patients who yielded figures from 5 to 10 mg., 11 were dead within seventeen days, averaging six days. Three others have since died. One of the latter finally succumbed to a cerebral hemorrhage after having attained normal blood chemical values. Of 21 patients with readings ranging from 2.5 to 5 mg., 16 are now dead.

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OBSERVATIONS ON THE ACTION OF GERMANIUM DIOXIDE  
IN PERNICIOUS ANEMIA.

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THE experimental work conducted by Hammett, Nowrey and Müller on the erythropoietic action of germanium dioxide<sup>1</sup> suggested to me to make some clinical observation upon the action of this substance in cases of pernicious anemia. The abovenamed investigators showed that the administration of the germanium to albino rats led to "a marked and statistically valid rise in the number of erythrocytes." Their experimental work was suggested by the close relationship existing between the positions of germanium and arsenic in the periodic system, where they are adjacent in series. They also showed that germanium possesses a toxicity approximately twenty-two times less than that of arsenic. They administered subcutaneously to animals 180 mg. of germanium per kilo of body weight with no harmful effects, while arsenic exhibits fatal results at a rate of 8 mg. per kilo of body weight.

Müller and Iszard<sup>2</sup> published observations upon the action of

<sup>1</sup> *Jour. Exper. Med.*, 1922, **19**, 173.<sup>2</sup> *AM. JOUR. MED. SCI.*, 1922, **153**, 364.

germanium dioxide. The work was conducted upon the guinea-pig, rabbit, dog and one apparently normal man. They used a stable, saturated solution containing 0.004684 gm. of germanium dioxide per 1 cc, representing "the true solubility of the pure oxide in water." The lastnamed authors also made elaborate and extremely valuable determinations upon the cumulative effect and elimination of the substance.

The present paper is based upon observations made in 3 cases of pernicious anemia. The accompanying tables indicate the exact blood findings in each case. In my experience the results have been very disappointing and, because of the tremendous expense of this product, it seemed to me wise to report the findings, even though the experience is comparatively limited.

The diagnosis in the cases recorded seemed absolutely certain. The characteristic high color index was present in each one, normoblasts and megaloblasts were present in the blood smears. Roentgen-ray and all other modes of investigations failed to point to any other diseased process. In 1 case the diagnosis was verified at autopsy.

All hematinic medications (iron, arsenic, bone-marrow, etc.) were discontinued one week prior to the administration of the germanium, and were not exhibited until three weeks after the last dose of the drug was given.

In all 3 cases the germanium was administered at the rate of 100 mg. per kilo of body weight.

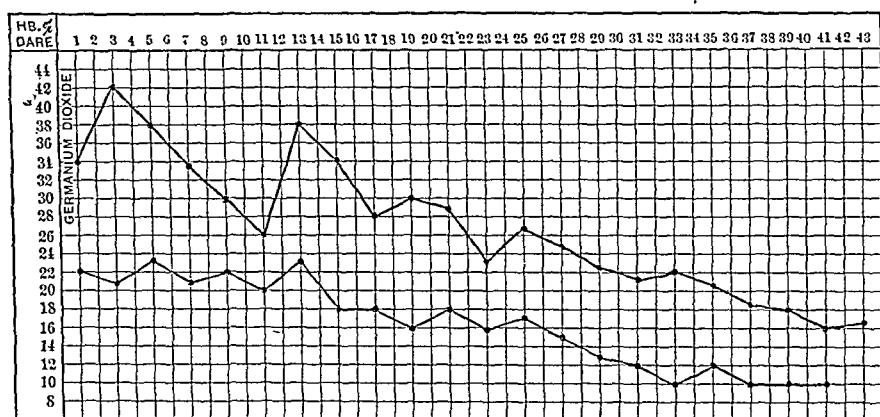


CHART I.—Hemoglobin and red blood cell count in Case I. (H. K.)

CASE I.—H. K., male, aged forty-one years; pernicious anemia of two years' duration. Patient was previously transfused several times with temporary amelioration of condition. At the time the administration of the germanium was started, the patient's hemoglobin was 22 per cent and the erythrocytes were 1,100,000. 100 mg. of germanium per kilo of body weight was administered and



a total of 5 gm. was administered in the course of three weeks. Approximately, 300 mg. was given hypodermically twice a week, while the rest of the substance was administered in solution by mouth. In spite of this treatment, the patient's condition continued to grow worse. The hemoglobin fell to 10 per cent (Dare) and the erythrocytes numbered 670,000.

TABLE I. DETAILS OF BLOOD EXAMINATION IN CASE I (H. K.)

Day No.	Hb.	R. B. C.	W.B.C.	Poly.	Lymph.	Mon.	Eos.	Bas.	Nucl. Reds.
1 . . .	22	1,100,000	5400	61	30	7	1	1	Many.
3 . . .	21	1,300,000	5600	60	28	10	2	0	"
5 . . .	23	1,200,000	5200	58	34	7	1	0	"
7 . . .	21	1,080,000	4800	64	32	3	0	1	"
9 . . .	22	1,000,000	5200	66	30	4	0	0	"
11 . . .	20	1,000,000	6000	60	28	9	2	1	"
13 . . .	23	1,200,000	6100	59	34	6	1	0	"
15 . . .	18	1,000,000	5400	54	32	12	1	1	"
17 . . .	18	950,000	5200	50	38	10	2	0	"
19 . . .	16	1,000,000	4800	58	36	5	0	1	"
21 . . .	18	960,000	5100	63	32	4	1	0	"
23 . . .	16	840,000	4600	62	30	7	1	0	"
25 . . .	17	920,000	4200	70	19	9	1	1	"
27 . . .	15	860,000	5200	64	26	8	1	1	"
29 . . .	13	820,000	4000	63	27	9	1	0	"
31 . . .	12	790,000	4800	59	30	1	0	1	Numerous.
33 . . .	10	800,000	4400	62	29	8	1	0	"
35 . . .	12	760,000	5400	58	31	9	1	0	"
37 . . .	10	720,000	6000	60	33	7	0	0	"
38 . . .	10	700,000	4100	64	31	4	1	0	"
41 . . .	10	650,000	4800	65	30	4	1	0	"

CASE II.—B. D., female, aged forty-six years; pernicious anemia. This patient was first seen in March, 1922. At the time of the first examination the hemoglobin was 16 per cent; erythrocytes, 1,200,000; leukocytes, 5200; with a differential count showing polymorphonuclears, 54 per cent; lymphocytes, 40 per cent; large mononuclears, 5 per cent; eosinophiles, 1 per cent; many normoblasts and megaloblasts, marked granular degeneration of the erythrocytes and polychromatophilia. The patient was put on germanium dioxide and treated essentially the same as in the first patient. There was no improvement following the administration of the compound (Table II). After administering the germanium for three weeks it was discontinued and three weeks later iron cacodylate,  $\frac{1}{2}$ -grain ampoules, was commenced intramuscularly, administered twice weekly. Considerable improvement was observed at the end of two weeks and blood changes became apparent very promptly.

TABLE II. HEMOGLOBIN AND RED BLOOD CELLS IN CASE II (B. D.)

Day No.	Hemoglobin Per cent	Red Blood Cells	Day No.	Hemoglobin Per cent	Red Blood Cells
1	16	1,200,000	33	10	1,050,000
3	14	1,100,000	35	11	920,000
5	16	1,100,000	37	10	940,000
7	14	1,200,000	39	12	980,000
9	12	1,000,000	41	14	1,000,000
11	13	1,050,000	43	13	1,060,000
13	15	1,050,000	45	14	1,900,000
15	13	1,000,000	47	15	1,120,000
17	11	980,000	49	16	1,400,000
19	13	1,100,000	51	14	1,610,000
21	14	1,000,000	53	18	1,880,000
23	15	960,000	55	20	1,900,000
25	12	940,000	57	21	1,860,000
27	11	980,000	59	22	2,000,000
29	10	1,000,000	61	24	2,100,000
31	9	1,000,000	63	24	1,980,000

TABLE III. HEMOGLOBIN AND RED BLOOD CELLS IN CASE III (W. W.)

Day No.	Hemoglobin Per cent	Red Blood Cells	Day No.	Hemoglobin Per cent	Red Blood Cells
1	16	1,050,000	33	12	1,000,000
3	16	1,040,000	35	14	1,110,000
5	15	1,000,000	37	15	1,200,000
7	14	1,100,000	39	16	1,210,000
9	16	1,200,000	41	16	1,200,000
11	17	1,210,000	43	17	1,250,000
13	18	1,240,000	45	18	1,260,000
15	16	1,200,000	47	20	1,280,000
17	16	1,100,000	49	22	2,000,000
19	15	1,120,000	51	24	2,200,000
21	14	1,200,000	55	25	2,200,000
23	14	1,100,000	58	24	2,300,000
25	13	1,100,000	62	23	2,400,000
27	12	1,050,000	65	26	2,000,000
29	12	1,100,000	68	28	2,400,000
31	13	1,100,000			

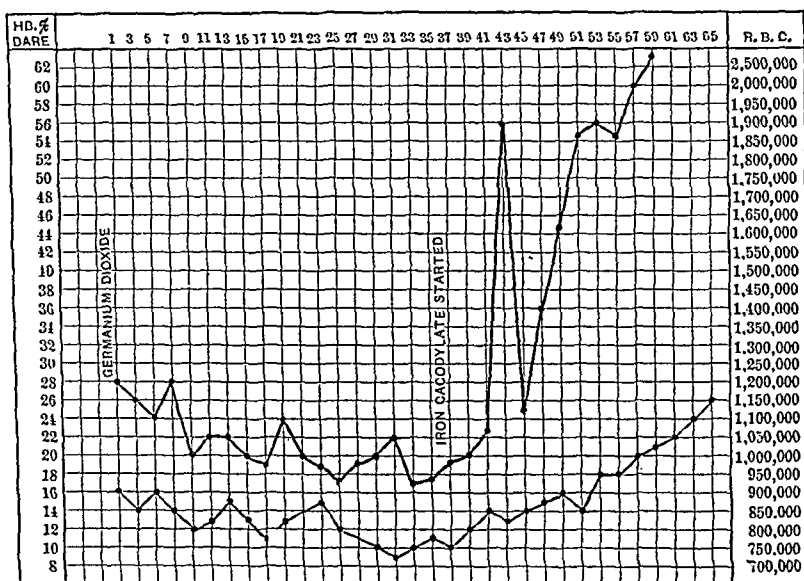


CHART II.—Hemoglobin and red blood cells in Case II (B. D.) showing effect of germanium and iron cacodylate respectively.

CASE III.—W. W., male, aged thirty-eight years; pernicious anemia. From the history of the case, the patient has had two previous exacerbations. He had the usual hematinic remedies, but no hypodermic administrations of iron and arsenic; no transfusions. The patient had no medication whatever for three weeks prior to the time when he was first seen. At the first examination the hemoglobin was 16 per cent (Dare); erythrocytes, 1,050,000; leukocytes, 4800; with a differential count of polymorphonuclears, 61 per cent; lymphocytes, 31 per cent; large mononuclears, 6 per cent; eosinophiles and basophiles, each 1 per cent; a moderate number of normoblasts and megaloblasts; marked granular degeneration and polychromatophilia. The germanium was administered as in Case I, and 4.5 gm. were used in four weeks' time.

Three weeks after the last dose of germanium, iron cacodylate,  $\frac{1}{2}$ -grain ampoules, was administered hypodermically twice a week for three weeks. Table III shows the details of the blood findings in this case.

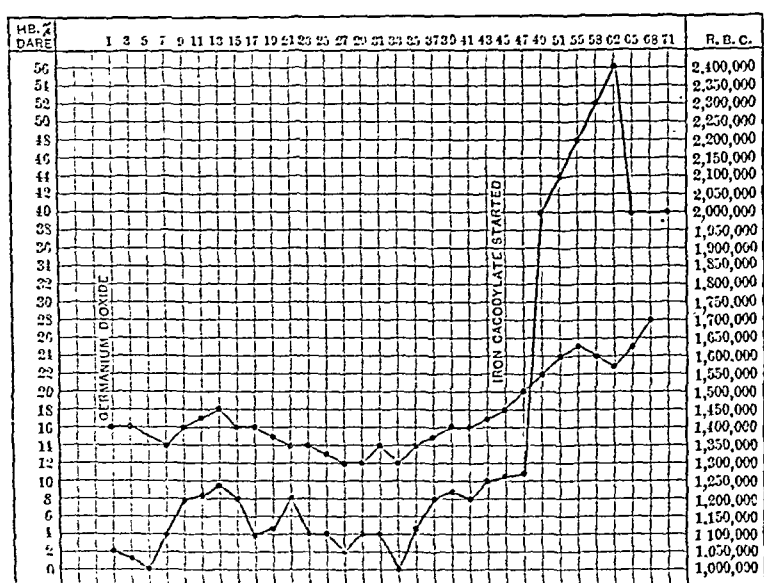


CHART III.—Hemoglobin and red blood cells in Case III (W. W.) showing effect of germanium and iron cacodylate respectively.

**Summary and Conclusions.** 1. Germanium dioxide, obtained from a reliable source, was employed in 3 cases of pernicious anemia. One of the cases was what might be called far advanced and the other 2 moderately advanced cases.

2. Diagnosis of pernicious anemia seemed certain in all of the cases. In 1 case it was verified at necropsy.

3. No clinical improvement was noticed in any of the cases and

the hemoglobin and erythrocytes showed no increase during the period of observation.

4. Arsenic and iron, administered hypodermically after the germanium was stopped, lead to an increase of hemoglobin and erythrocytes, also to symptomatic amelioration.

5. In pernicious anemia, germanium dioxide when administered by mouth and hypodermic injection led to no beneficial results. Arsenic and iron seemed definitely superior to germanium in this disease.

### THE ANTISEPTIC AND BACTERICIDAL PROPERTIES OF ISOPROPYL ALCOHOL.

BY DUDLEY H. GRANT, M.S.

ELIZABETH, N. J.

ISOPROPYL alcohol (also known as secondary propyl alcohol, dimethyl carbinol and petrohol) has been placed on the market in commercial quantities only during the last two or three years. In the United States, it is a by-product of the petroleum and natural gas industries, while in Germany it is produced by the reduction of acetone, which is made by a series of reactions from calcium carbide.

Isopropyl alcohol boils at  $82.26^{\circ}\text{C}.$ , and has a density of 0.7808 at  $\frac{25}{4}^{\circ}$ . Like ethyl alcohol, it forms a constant-boiling mixture with water. This mixture contains 91.1 per cent by volume of isopropyl alcohol, boils at  $80.4^{\circ}\text{C}.$ , and has a density of 0.8158 at  $\frac{20}{4}^{\circ}$ . This is the form in which the alcohol is usually marketed.

Isopropyl alcohol is similar in many of its properties to ethyl alcohol, though it appears, according to what few data have been published,<sup>1</sup> to produce no exhilarating effect when ingested, and has, moreover, an unpleasant taste, except in high dilution. No motive could, therefore, exist for attempting to employ it as a beverage.

The entry of isopropyl alcohol into commerce and its suggested use as a substitute for ethyl alcohol in cosmetics and external medicine has raised the question of its physiological properties.

The toxicity of isopropyl alcohol toward higher animals has been investigated by Macht,<sup>2</sup> Burton-Opitz,<sup>1</sup> Boruttau<sup>3</sup> and a number of earlier observers. Their results, obtained by various methods on a number of different animals, indicate that isopropyl alcohol is somewhat more toxic than ethyl alcohol, but not more than twice as toxic as ethyl alcohol. Its toxicity is slightly less than that of the isomeric normal propyl alcohol, and much less than that of the butyl and amyl alcohols. This is in accordance

with the well-known law of Richardson, which states that the toxicity of alcohols increases with their molecular weights.

Ingested isopropyl alcohol does not produce an acute secondary intoxication, due to its metabolic products, as does methyl alcohol. It has been shown, furthermore, to have no noticeable harmful effect upon the human skin.<sup>1 3</sup>

The comparative bactericidal power of isopropyl alcohol might be expected to run roughly parallel to its toxicity. That this is the case is confirmed by the three published investigations bearing on this subject which a search of the literature has revealed.

Wirgin<sup>4</sup> performed a long series of comparative experiments upon the power of various alcohols, in various concentrations, to inhibit the growth of, and to kill, cultures of *Micrococcus pyogenes aureus*.

Growth in bouillon cultures at 37° C. was inhibited by 8 per cent of methyl alcohol, 6 per cent of ethyl, 4 per cent of propyl (either normal or iso-), 2 per cent of butyl (either normal or iso-) or 1 per cent of normal amyl alcohol.

Suspensions of *Micrococcus pyogenes aureus* were dried on quartz pebbles and subjected to the action of various alcohols in different concentrations for various lengths of time, then rinsed, shaken with sterile water and plated out on agar. Isopropyl alcohol, at a concentration eight times normal (*i. e.*, 48 per cent), effected complete sterilization in five minutes, while ethyl alcohol of the same molecular concentration did so in ten minutes, and methyl alcohol failed to sterilize during fifteen minutes, as did 1 per cent phenol. A normal (*i. e.*, 6 per cent) solution of isopropyl alcohol failed to kill off the dried cocci in fifteen minutes. Propyl alcohol, either normal or iso-, in 20 per cent concentration, killed the cocci in a few minutes, while 20 per cent ethyl alcohol hardly did so in twenty-four hours.

Wirgin also investigated the optimum concentration of methyl, ethyl and normal propyl alcohols for effectiveness against *Micrococcus pyogenes aureus* dried on silk threads and in moist suspension. One minute's immersion secured sterilization of the silk threads in the case of 60 per cent ethyl and methyl alcohols, and in propyl alcohol of all concentrations from 20 to 60 per cent, inclusive. Highly concentrated alcohols (*i. e.*, stronger than 70 or 80 per cent) were found, as is well known, to be ineffective against dried bacteria. The minimum sterilizing concentration, for one minute's action, against moist cocci, was 60 per cent for methyl alcohol, 50 per cent for ethyl and 20 per cent for propyl. In this case, the higher concentrations were also effective. Unfortunately, isopropyl alcohol was not used in this test, but the close similarity between the bactericidal properties of the two propyl alcohols observed by Wirgin in all the other tests makes it probable that its effective concentration would be about the same.

Wirgin found the bactericidal action of the alcohols to be especially notable when *Micrococcus pyogenes aureus* dried in blood serum was employed. The penetrating property of alcohols, together with the fact that they do not coagulate serum proteins, made their solutions (at optimum concentration) distinctly more effective than 0.2 per cent mercury bichloride or 5 per cent formalin, and approximately equal to 3 per cent phenol, 2.5 per cent cresol plus soap, or 0.1 per cent iodine trichloride solutions.

Considering aqueous alcohols as a class, Wirgin ranks 30 per cent propyl or isopropyl first, 60 per cent ethyl next, 60 per cent methyl next, and saturated solutions of the higher alcohols next, in bactericidal efficiency. The butyl and amyl alcohols, while more effective in equal concentration than the lower alcohols, are not, like them, miscible with water in all proportions, and are consequently limited in application.

From the standpoint of practical application, the propyl alcohols (isopropyl and normal propyl) occupy an especially favorable position in that they are the alcohols of the highest molecular weight that are still miscible with water in all proportions.

Bernhardt, Director of the Bacteriological Laboratory of the Friedrichshain Hospital, Berlin, has recently published<sup>5</sup> an investigation of isopropyl alcohol as a means for disinfecting the hands in surgical and gynecological practice. *Staphylococcus pyogenes aureus*, *Bacillus coli communis*, *Bacillus anthracis* and *Bacillus subtilis* were used as test organisms. Inhibition of bacterial growth was effected at between 3 and 6 per cent concentration of isopropyl alcohol. Dilute isopropyl alcohol killed dried anthrax bacilli and staphylococci in two to five minutes. A 40-per-cent concentration of isopropyl alcohol was found to be approximately equivalent to 60 per cent ethyl alcohol.

Bernhardt then carried out a series of practical tests by soiling the hands of several subjects with *Bacillus coli* cultures, allowing them to dry and then, without washing, rubbing them with isopropyl alcohol (20 cc on gauze; later, 10 cc was found sufficient). One finger, as a control, untreated with alcohol, but dipped into nutrient agar, demonstrated extreme contamination, over 20,000 bacteria per finger.

The alcohol, in 80 per cent and 60 per cent concentration, was rubbed upon the hands until it evaporated. In a series of 20 experiments, this resulted in complete sterilization in 60 per cent of the cases, extensive reduction (less than 10 surviving bacilli) in 20 per cent, and considerable reduction (10 to 1000 surviving bacilli) in 20 per cent. This approximates the action of ethyl alcohol. Isopropyl alcohol is effective, however, in lower concentrations than is ethyl. Bernhardt emphasizes, as have previous authors, the wide variation in individual hands, with respect to ease of disinfection. He recommends that isopropyl alcohol of 50

per cent be used upon dry hands, and of 70 to 80 per cent upon moist hands, and concludes that it is a complete substitute for ethyl alcohol, for this purpose. He did not, apparently, investigate the effectiveness of isopropyl alcohol at its optimum concentration, *i. e.*, 30 to 50 per cent.

Seifert<sup>6</sup> tested the fermentability of various alcohols by *Bacterium pasteurianum* and *Bacterium kuetzingianum*, two acetifying organisms isolated by Hansen from *Mycoderma aceti*. Isopropyl alcohol showed a marked inhibiting effect upon these bacteria, no growth being observed during eight weeks in the presence of 1 per cent of the alcohol. Yeast decoction and unhopped beer wort were used as media. The same organisms fermented 5 per cent ethyl, 3 per cent normal propyl and 1 per cent normal butyl and isobutyl alcohols, and grew in a medium containing 2 per cent methyl alcohol, though without oxidizing the alcohol. Toward the vinegar-forming bacteria, therefore, isopropyl alcohol appears to have the greatest antiseptic power of all the lower alcohols.

Of interest in this connection is the work of Pringsheim,<sup>7</sup> who demonstrated that isopropyl alcohol is formed by an organism, *Clostridium americanum*, isolated by him from potatoes, and producing also normal butyl alcohol and butyric acid when grown on potato mash. This datum confirms the scattered and questioned references<sup>8</sup> to the presence of isopropyl alcohol in fusel oil, which is shown to be due to an abnormal fermentation involving butyric acid bacilli.

While not dealing with isopropyl alcohol, the work of Saul<sup>9</sup> has an inferential bearing. This investigator subjected sporulated cultures of *Bacillus anthracis*, as well as other organisms, to the action of boiling alcohols of different concentrations. He employed only methyl, ethyl and normal propyl alcohols, and found all three to be useless when anhydrous, but effective in lower concentrations, when the duration of boiling was sufficient. The aim of Saul's work was to find an easy and effective method for sterilizing surgical sponges, and he concluded that boiling 30 per cent propyl alcohol was the best agent tried. It is a plausible assumption that isopropyl alcohol might serve as well.

Since isopropyl alcohol has come into commerce in this country, samples of it have been distributed to several physicians and hospitals, for use as a massage medium and surgical antiseptic, with general satisfaction. It has also found employment as a preservative for museum specimens and for surgical catgut.

**Summary and Conclusions.** 1. Isopropyl alcohol is a nonpotable alcohol, somewhat more toxic than ethyl alcohol, but not more than twice as toxic as ethyl alcohol.

2. Isopropyl alcohol is a more powerful bactericide and antiseptic than ethyl alcohol toward the organisms so far studied (*Staphylococcus pyogenes aureus*, *Bacillus coli communis*, *Bacillus*

anthracis, *Bacillus subtilis* and acetic acid bacteria). It is most effective in concentrations of 30 to 50 per cent.

3. Since it is not liable to be diverted for beverage use, and is not subject to burdensome taxes and restrictions, isopropyl alcohol may advantageously replace ethyl alcohol, under some circumstances, as a surgical antiseptic and preservative.

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#### STUDIES ON THE REACTIONS OF ASTHMATICS AND ON PASSIVE TRANSFERENCE OF HYPERSUSCEPTIBILITY.

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1. CUTANEOUS AND OTHER REACTIONS IN BRONCHIAL ASTHMA. According to investigations by Walker,<sup>1</sup> Rackemann, Freeman, de Besche and others, certain forms of asthma are regarded as expressions of hypersusceptibility to foreign proteins that may gain entrance into the body. Such forms of asthma might be called anaphylactic asthma. In this article, certain results are reported of investigations on asthmatics by means of protein extracts of timothy pollen, of substances from various animals (horse, dog, cat, chicken, sheep, crabs, lobster, honey, milk, egg, fish, potato, oats, rye, rice, staphylococci, streptococci, *Micrococcus tetragenus*, strawberries, nuts, apples, pears). Altogether, cutaneous reactions of 86 asthmatics have been studied. Careful clinical examination with roentgen photographs and special examination of the nose and throat were made in each case of suspected asthma, and all cases of dyspnea that might be associated with



cardiorenal diseases and organic lung changes have been eliminated. Paroxysmal dyspnea with sibilant rales in the chest without any demonstrable anatomical cause has been the standard

TABLE I.—CUTANEOUS AND OTHER REACTIONS IN THIRTY-FIVE ASTHMATICS.

Patients.			Timothy pollen.	Horse.			Cat.			Dog.			Egg.	Fish.	Wheat.	Staphylococci.	Streptococci.	M. tetragenus.	Strawberries.	Nuts.	Apples, pears.	Crab.	Honey.
No.	Age.	Sex.		Serum.	Walker's extract.*	Eye (do Besche).	Serum.	Walker's extract.*	Eye (do Besche).	Serum.	Walker's extract.*	Eye (do Besche).											
1	45	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
2	24	F	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
3	25	F	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
4	42	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
5	22	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
6	49	M	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
7	29	F	○	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
8	30	M	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
9	37	F	○	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
10	10	M	+	○	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
11	14	M	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
12	45	M	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
13	16	F	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
14	7	F	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
15	22	M	+	○	○	+	○	○	○	○	○	+	+	○	○	○	○	○	○	○	○	○	○
16	35	M	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○
17	27	M	○	○	○	○	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
18	38	M	○	○	○	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
19	22	F	+	○	+	+	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○
20	29	M	+	+	+	+	+	+	+	+	+	+	○	○	○	○	○	○	○	○	○	○	○
21	43	F	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○
22	24	F	+	○	○	+	○	○	+	○	○	○	○	○	○	○	○	○	○	○	○	○	○
23	22	F	+	+	+	+	○	○	○	○	○	○	○	+	○	○	○	○	+	○	○	○	○
24	9	M	+	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○
25	7	M	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	+	○	○
26	11	M	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○	○	○
27	52	M	+	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○	○	○	○	○
28	30	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○
29	26	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○
30	40	F	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	○	+	○	○	○	○
31	70	M	+	○	+	+	○	○	○	○	○	○	○	○	+	+	+	○	○	○	○	○	○
32	52	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
33	45	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
34	52	M	○	○	○	○	○	○	○	○	○	○	○	○	○	+	+	○	○	○	○	○	○
35	51	F	○	○	○	○	○	○	○	○	○	○	○	○	+	+	+	○	○	○	○	○	○

In addition, all 35 patients were negative to chicken, sheep, milk, potato, oats, rye, rice, lobster, crawfish.

\* Prepared by Arlington Chemical Company.

for the diagnosis in each case. As shown in Table I, which gives the positive results, the most frequent reaction was obtained with extracts of horse proteins, 23 in all, and in some of these cases,

reactions were obtained also with other substances. It is interesting that the results corresponded either with the experiences of the patients themselves as to the causes of their asthma or with results of experiments that I made upon the basis of the reaction. It appears that several substances may cause asthma in the same patient: Patient 23 becomes asthmatic from emanations of flowers and from contact with horses as well as on eating fish or strawberries, and Patient 25, a seven-year-old boy, is made asthmatic on eating eggs and apples. A sister of this patient, upon eating these things, develops urticaria but not asthma. Patient 15 develops asthma and coryza on contact with horses and dogs; Patient 18, on contact with horses and cats; and Patient 20 on contact with horses, dogs and cats. The patients reacting to bacterial extracts were old asthmatics with chronic bronchitis. Three patients reacted to extracts of nuts; one of them developed typical asthma upon eating nuts, with swelling of the oropharyngeal mucous membrane and of the conjunctiva and running of the nose; the others developed less-marked pulmonary symptoms but marked oronasopharyngeal and conjunctival symptoms upon eating nuts; one developed similar symptoms also from eating apples and pears.

Reactions were made according to certain methods of my own also. The patients who were susceptible to extracts of horse materials were tested for skin reactions to horse serum and for conjunctival reactions upon touching the conjunctiva with a finger that had been passed over the hair of a horse or other animal, the finger thus carrying a little dandruff or sweat. This conjunctival reaction is referred to hereafter as the eye reaction (de Besche). Of the 23 asthmatics giving reactions to horse extracts, 10 gave cutaneous reactions to horse serum, 17 reacted to Walker's extracts, and all gave the eye reaction. These tests were made at the same time in each case. Of the patients sensitive to cat material, 3 gave positive reactions to all tests, 1 only the eye reaction; the details of the reactions to dog extract may be seen in the Table. On the whole, in cases of asthma depending apparently upon contact with horses, cats and dogs, the eye reaction gives the largest number of positive results, next the test according to Walker's method, while less than half reacted to horse serum on cutaneous injections. Comparing the degrees of hypersusceptibility of the patients giving the eye reaction and skin reaction with horse serum, those reacting to the latter must be regarded as the more sensitive. It has been said that asthmatics that give cutaneous reaction to horse serum should not be injected with horse serum, because of the danger of violent symptoms, whereas asthmatics that give reactions with Walker's extracts only may be injected without danger. All my cases of horse asthma have been tested for cutaneous reactions to sheep serum,

but with uniformly negative results, suggesting that antidiphtheria serum developed in sheep would be free from danger. Certain patients hypersusceptible to other substances were tested further as to eye and skin reactions with the material itself or with juice pressed out of it, and in only 2 cases, giving positive reactions, was there failure to react to Walker's extracts.

Most of the patients in whom positive reactions developed knew beforehand the conditions under which asthmatic symptoms usually would arise, but this was not true of all. Thus, Patient 4 and Patient 20 did not realize until they were eighteen and twenty-seven years old, respectively, that their asthma depended upon contact with certain animals. Others (Patients 2, 11, 15 and 26) knew nothing of the influence the materials to which they reacted played in the production of the asthma from which they suffered, and they derived great benefit from the knowledge thus obtained. It should be noted that, as my material is selected material, it should not be made the basis for any statistics of the different kinds of asthma. Some patients seem to have known since early childhood that they were susceptible to contact with horses or to certain foods, while to others this did not become apparent until much later. Patient 4, a woman, aged twenty-four years, who lived in the country and came in close contact frequently with horses, did not begin to suffer from asthma until seventeen years of age, and shortly afterward she realized that the asthma was connected in some way with horses. Three patients are farmers, who began to suffer from asthma, due to contact with horses, after reaching adult age. Patient 30, a woman, aged forty years, could eat apples, pears and nuts without harm until thirty-six years of age, when she began to suffer from paroxysms of asthmatic symptoms with increased nasal secretions and swelling of the eyes, and in the course of the next two or three years it became apparent to her that these symptoms arose only after the consumption of the articles mentioned. In many cases of hay fever and asthma, a familial disposition to hypersusceptibility is present because the majority of the patients state that several members of their families suffer from these diseases. The similarity of these asthmatic conditions, particularly horse asthma, to experimental anaphylaxis is shown by the fact that one patient, who suffered from anaphylactic shock after injection of antidiphtheria (horse) serum, remained free from the usual asthmatic symptoms when in contact with horses for about three months; in other words, a condition of antianaphylaxis was produced by the injection of the horse serum. Bacon and Wright<sup>2</sup> made similar observations, and Walker and others have shown that small quantities of horse proteins may produce a temporary insusceptibility in horse asthmatics. The remarkable case of asthma, following injection of horse serum, described by Walker, seems so far to remain quite unique. As

stated in greater detail in the following, I have succeeded in making guinea-pigs susceptible to horse serum and also to cat serum, by injecting them with the serum of patients with horse and cat asthma. These results are quite analogous to the noteworthy case, described by Ramirez,<sup>3</sup> of the patient who was transfused with blood and subsequently developed asthma dependent upon contact with horses. It was found then that the donor suffered from a pronounced form of horse asthma.

2. PASSIVE TRANSFERENCE OF HYPERSUSCEPTIBILITY BY THE SERUM OF CERTAIN ASTHMATIC PERSONS. When the blood of an animal, made hypersensitive by the injection of a foreign protein, is injected into a normal animal, the normal animal may become hypersensitive to the same protein. This is passive anaphylaxis. As a rule, some hours must elapse after the injection before passive anaphylaxis becomes demonstrable; in the case of guinea-pigs, from six to twenty-four hours may elapse; in dogs, Richet found that passive anaphylaxis could be demonstrated after two hours. It is believed that this latent period corresponds to the time required for the antistances in the injected serum to become anchored to the cells of the tissues. It has been found possible to transfer anaphylactic conditions in man to guinea-pigs. Thus, Grysez and Bernard,<sup>4</sup> as well as Achard and Flandin,<sup>5</sup> found that the blood of patients, injected with therapeutic serum and who, on that account, had become hypersensitive to the serum, when injected into guinea-pigs, made them anaphylactic with respect to the same serum. Longcope and Rackemann<sup>6</sup> obtained similar results with the serum of patients who had been injected with large quantities (180 to 360 cc) of antipneumococcus serum (horse serum); in a large number of cases, the guinea-pigs so injected became anaphylactic with respect to horse serum. In a case of urticaria in man from eating pork, Bruch,<sup>7</sup> by injecting the patient's serum into guinea-pigs, rendered them hypersensitive to swine serum. Schultz and Larson<sup>8</sup> report cases of hypersusceptibility to milk in children and the production of passive anaphylaxis in guinea-pigs by the injection of the serum of such children. The question arises whether the serum of an asthmatic patient, who is hypersensitive with respect to a particular protein, can render guinea-pigs anaphylactic to the same protein. As only scattered observations appear to have been made in regard to this question, it seemed to me advisable to publish the results of further observations.<sup>9</sup> In most of my cases, it concerns persons who were hypersensitive to emanations from horses; in 1 case, the patient was hypersensitive to cats. From 1 to 5 cc of the serum of the patient was injected intraperitoneally in guinea-pigs and after twenty-four to forty-eight hours, the guinea-pigs were then injected with horse or cat serum, usually in quantities of 0.5 cc intravenously or of 3 to 5 cc intraperitoneally. Furthermore, 0.1 cc of serum was injected

intracutaneously in the guinea-pigs with a view to studying the local reactions.

CASE I.—Woman, aged twenty-three years, suffered from horse asthma since her sixteenth year. By going into a stable for horses, driving with horses, etc., marked dyspnea would develop that might last for several days. When removed from horses and things that had been in contact with horses, she was free from symptoms. Other animals did not have any such effects. When the conjunctiva was touched with the finger that previously had stroked a horse, a strong reaction would develop; she also gave a marked cutaneous reaction with Walker's extract of horse dandruff and with horse serum. The patient's serum, 5 cc, was injected intraperitoneally into a guinea-pig, and twenty-four hours later the guinea-pig received 0.5 cc of horse serum intravenously; in five minutes, marked anaphylactic shock developed. Another guinea-pig received 2.5 cc of the patient's serum intravenously, and forty-eight hours later 0.5 cc of horse serum intravenously; this animal also developed definite symptoms of anaphylactic shock. Before being injected intravenously, both animals received 0.1 cc of horse serum intracutaneously, and in 1 of them a large wheal, 1 cm. in diameter, developed, but the other gave no definite reaction.

CASE II.—Man, aged thirty-three years, asthmatic from earliest childhood when in contact with horses; suffered also from hay fever and asthmatic attacks on eating strawberries. A strong conjunctival reaction developed from the touch of a finger that had been passed over the hair of a horse. He gave a marked cutaneous reaction with Walker's extract of horse dandruff and with horse serum as well as with extracts of pollen and strawberries. The patient's serum, 5 cc, was injected into a guinea-pig intraperitoneally; twenty-four hours later 3 cc of horse serum were injected intraperitoneally and was followed by marked anaphylactic shock in fifteen minutes. A similar result followed the injection of 0.5 cc of horse serum intravenously in another guinea-pig which had received 3 cc of the patient's serum intraperitoneally forty-eight hours before. In 1 of the animals, 0.1 cc of horse serum produced, on intracutaneous injection, a large wheal.

CASE III.—Man, aged thirty years, asthmatic from earliest childhood when near horses; strong conjunctival and cutaneous reactions developed when tested, as the previous two patients; guinea-pigs injected with the patient's serum intraperitoneally, 5 cc in each case, and reinjected in the same way with the same quantity of horse serum in twenty-four hours, developed marked anaphylactic shock, and in one of the animals a large wheal developed on intracutaneous injection of 0.1 cc of horse serum.

CASE IV.—Man, aged thirty-eight years; since childhood swelling of the conjunctiva and cutaneous wheals developed whenever he came in contact with cats; similar symptoms, but less marked, also developed from contact with horses; asthmatic symptoms from time to time. Touching the conjunctiva with a finger after stroking a cat gave rise to redness, edema, and flow of tears; after a similar test after stroking a horse, redness and itching developed. When scratched by a cat, large wheals would develop. After the intraperitoneal injection of 5 cc of the patient's serum and forty-eight hours later an injection of 3 cc of cat serum, marked symptoms of anaphylactic shock developed, while the intraperitoneal injection of 5 cc of cat serum in a fresh guinea-pig was without any special effect.

CASE V.—Man, aged forty-three years, horse asthma from childhood and also suffered from hay fever, sometimes with marked asthmatic symptoms. He gave strong conjunctival and cutaneous reactions to horse proteins. A guinea-pig injected intraperitoneally with 1 cc of the patient's serum, and twenty-four hours later with 0.5 cc of horse serum intravenously, developed marked anaphylactic shock; another guinea-pig injected intraperitoneally with 5 cc of the patient's serum, and forty-eight hours later with 5 cc of horse serum, developed only some dyspnea and a subnormal temperature. Both these animals developed large wheals in the skin on the intracutaneous injection of 0.1 cc of horse serum twenty hours after the injection of the patient's serum.

CASE VI.—A man, aged forty-two years, asthmatic since childhood, apparently dependent upon horse emanations; marked eye reaction and marked skin reaction to extract of horse dandruff, but no reaction upon intracutaneous injection of horse serum. Guinea-pigs injected intraperitoneally with 5 cc of the patient's serum gave no anaphylactic reaction upon intravenous or intraperitoneal injection of horse serum twenty-four hours later, and no cutaneous reaction to horse serum.

CASE VI *b*.—Woman, aged twenty-nine years, asthmatic at times as child and since eighteen years old has suffered from asthma when in contact with horses; she gave a strong eye reaction upon touching conjunctiva with a finger that had been passed over a horse; also cutaneous reaction with extract of horse dandruff, but not with horse serum; no anaphylactic symptoms and no cutaneous reaction in guinea-pigs injected with the patient's serum and reinjected with horse serum.

CASE VII.—Man, aged forty-four years, asthmatic since twenty years old when in contact with horses; strong eye reaction to finger

passed over the skin of a horse and strong skin reaction with extract of horse dandruff; no anaphylactic symptoms or cutaneous reaction upon injection of horse serum in guinea-pigs previously injected with the patient's serum.

CASE VIII.—Man, aged thirty-eight years, asthmatic since sixteen years old, depending upon horse emanations; his reactions were similar to those in Case VII, and the patient's serum did not render guinea-pigs anaphylactic to horse serum.

CASE IX.—Woman, aged twenty-three years, asthmatic since childhood from contact with horses; similar reactions as Cases VII and VIII; the patient's serum did not render guinea-pigs sensitive to horse serum.

In 4 cases, the serum of patients, suffering from asthma dependent on contact with horses, rendered guinea-pigs anaphylactic to horse serum. These patients gave eye and skin reactions to horse proteins. Analogous results were obtained in the case of 1 patient sensitive to cat emanations. In 5 other cases of horse asthma, the serum of the patient did not produce passive sensitization to horse serum in guinea-pigs. In these cases, the asthma appeared to be dependent upon horse emanations, but none of these cases gave any cutaneous reaction to horse serum, but all except one gave eye reactions by the de Besche method and skin reactions to horse dandruff. It appears that these patients were sensitive to substances in horse hair, dandruff and sweat and not to substances in horse serum.

I have emphasized that asthmatics,<sup>10</sup> in whom the disease appears to be dependent upon certain animal emanations, may give different local reactions, as observed also by others, some giving skin reactions with serum as well as with extract of hair and dandruff, while others do not react to the animal's serum. Whether this difference represents an essential difference in the nature of the conditions is difficult to say, but it would seem most reasonable to assume that it concerns differences in the degree of hypersensitiveness and that patients giving cutaneous reactions to serum are the more sensitive. This view is supported by my experiments in that in 4 instances of horse asthma and 1 of cat asthma, all these patients giving skin reactions to the corresponding serum, the patients' serum in each case produced passive anaphylaxis to horse serum in guinea-pigs.

As stated, Ramirez<sup>2</sup> describes an instance of a man who had not had asthma before, but who soon after transfusion began to have asthmatic attacks when in close contact with horses, and that it was found that the donor of the transfused blood suffered from horse asthma. In this case, the sensitive state was transferred

in the blood of one person to another. By means of the serum of asthmatics, I have succeeded in producing a local hypersusceptibility to horse serum in the skin of previously normal persons.

EXPERIMENT 1.—A man, aged forty-two years, was asthmatic since childhood upon coming in contact with horses; he gave a marked eye and skin reaction and reacted also to the cutaneous injection of horse serum. A perfectly healthy man, who did not suffer from asthma or urticaria, received 0.1 cc of the serum of the patient intracutaneously on the left forearm and also, for purposes of control, 0.1 cc of serum from a normal person and, in another place, 0.1 cc of salt solution. No reaction developed about any of these injections, and after twenty-four hours 0.1 cc of horse serum was injected intracutaneously in all the three places previously injected, and in the course of five minutes a large wheal, about 3 cm. in diameter, developed about the place in which the serum of the asthmatic patient had been injected. This wheal was surrounded by a hyperemic zone and itched greatly; it remained in full bloom for three or four hours and then disappeared fairly rapidly. The places injected with normal serum and salt solution showed no reaction from the injection of the horse serum.

EXPERIMENT 2.—Man, aged fifty-two years, has had hay fever since childhood, with asthma influenced by contact with horses; pronounced eye and skin reactions, as well as reaction to horse serum and to pollen; 0.1 cc of serum was injected intracutaneously in the arm of the patient's wife, also 0.1 cc from a normal person, and the same amount of salt solution; no reaction about any of the three points, and twenty-four hours later 0.1 cc of horse serum was injected intracutaneously, as in the previous case, with the result that an itching wheal, 4 cm. in diameter and surrounded by redness, developed about the point where the husband's serum had been injected; no reaction developed about the other points. In the other arm, also injected in three places in the same way, the injection of sheep serum twenty-four hours later did not produce any reaction. The subject of the experiment received 0.1 cc of the patient's serum intracutaneously in two other places and twenty-four hours later extract of pollen (Freeman's preparation) was injected in these places, and in one of them a large itchy wheal developed. The injection of pollen in other places of the skin gave no reaction.

EXPERIMENT 3.—Woman, aged thirty-six years, asthmatic since childhood, depending upon horses; sometimes, after contact with horses, urticaria would develop; marked eye reaction, as well as cutaneous reactions with extract of horse dandruff and horse serum; an experiment like that described in Experiment 1 was



made and with a similar result—the place where the patient's serum had been injected developed a large itching wheal upon the injection of horse serum twenty-four hours later.

**EXPERIMENT 4.**—Woman, aged twenty-eight years, asthmatic since childhood from contact with horses; marked eye and skin reactions; a sister of the patient, who did not have asthma, was injected intracutaneously with 0.1 cc of the patient's serum, in another place with the same quantity of normal serum, and in a third place with the same quantity of salt solution; twenty-four hours later 0.1 cc of horse serum was injected intracutaneously in all three places, but no reaction developed in any place.

**EXPERIMENT 5.**—Man, aged thirty-two years, asthmatic since ten years of age, apparently from sensitiveness to horses; he gave a marked eye reaction and skin reaction with extract of horse dandruff, but no reaction followed intracutaneous injection of horse serum; a brother, who was normal, was injected exactly in the same way as in Experiment 4, but no reaction developed.

In 3 of the experiments just described, the intracutaneous injection of serum from patients, suffering from asthma dependent upon substances from horses, produced a local hypersusceptibility to horse serum. This hypersusceptibility showed itself in the form of a wheal with hyperemia about the point where the horse serum was injected and where twenty-four hours before serum from the asthmatic patient had been injected. It seems quite clear that the asthmatic serum contained certain substances that produced a local hypersusceptibility.

These experiments and the experiments upon guinea-pigs show that certain asthmatics suffer from a condition that can be transferred passively. The patients with asthma, in which passive transfer of hypersusceptibility did not succeed, did not give any cutaneous reaction to horse serum, and may be regarded as less sensitive than those whose serum produced passive anaphylaxis.

Prausnitz and Kuster<sup>11</sup> report an instance of hypersusceptibility to fish protein, in which they produced a local hypersensitiveness in the skin of a normal person by the injection of the serum of the patient, but they did not succeed in similar experiments with the serum of hay-fever patients and of patients hypersusceptible to horse serum.

**Conclusion.** Taken in conjunction with the local skin and other reactions in asthmatics, the occasional severe symptoms of anaphylactic shock upon injection of asthmatics with horse serum and the demonstration in occasional cases of asthma of complement-binding bodies and precipitin in the serum, the results now presented, showing that the serum of asthmatics may be the means of trans-

ferring hypersusceptibility, strengthens materially the opinion that certain forms of asthma may be regarded as anaphylactic in nature.

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#### DIFFERENTIAL DIAGNOSIS OF DIABETES.

BY HENRY J. JOHN, M.D.,

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OFTEN a patient with no subjective complaint is referred to a specialist because his family doctor or the examiner of a life insurance company has found sugar in the urine, either once only or repeatedly. The patient appears to be in perfect health, offers no complaint, no symptoms are apparent and there are no pathological physical findings. An examination of the urine discloses no sugar and examination of the fasting blood sugar shows a normal content.

What can one do in such a case? What can be said to the patient to allay his fears of diabetes and at the same time guard him against a possible later development of diabetes, the signs of which are absent at the moment? Can one say simply "I find no diabetes; you're all right" and let the patient go, only to return in a year or two with fully developed diabetes? Or shall he be condemned as a diabetic, in spite of the present negative findings, judgment being based merely on the sugar found in the urine by the referring doctor or the insurance examiner? In the latter case after following a restricted diet for a year or two, the patient may consult another specialist who may settle his problem by saying: "You are not diabetic; eat anything you wish."

Perhaps in no other disease is the establishment of a positive diagnosis in the early and in the borderline cases so difficult or a mistaken diagnosis so fraught with danger as is the case with diabetes and a final diagnosis in these cases often requires more than the common measures which are accessible to a man in general practice. It is therefore of importance that the general practitioner and the medical examiner understand what measures are essential

for the final establishment of a diagnosis in doubtful cases, and why dependence cannot be placed on urine examination alone, or even on the evidence of a single fasting blood-sugar estimation.

The point to be established is the ability of the individual to utilize (metabolize and store) carbohydrates. The presence of sugar in the urine tells only that the kidneys are permeable to sugar and by itself alone does not even disclose at what blood-sugar concentration this "overflow" takes place; for the permeability of the kidneys to glucose varies with the individual, and in different individuals, therefore, sugar may be found in the urine at any blood sugar concentration between 53 and 256 mg. per 100 cc.

It follows therefore that a progressive study of the blood sugar content—the establishment of the glucose tolerance curve—is the only method by which the ability of the individual to utilize carbohydrates can be established with certainty. That is, upon the glucose tolerance curve depends the establishment of the diagnosis of diabetes; moreover, the glucose tolerance curve discloses also whether or not the individual may be liable to develop diabetes and thus becomes a valuable prophylactic guide.

To illustrate the application of this procedure the following cases are cited:

CASE I.—A little boy, aged seven years, was brought in from a neighboring state where a diagnosis of diabetes had been made by his family physician, this diagnosis being based on the presence of sugar in the urine after a period of general malaise of several weeks duration.

Routine examination at this time showed no sugar in the urine, and a fasting blood sugar of 84 mg. per 100 cc—a low normal. The boy's mother stated, however, that for the preceding few days the boy had had a restricted diet. Were we justified on the basis of this examination in stating that this was not a case of diabetes since there was no sugar in the urine and no increased blood-sugar content?

In spite of the fact that the urine and fasting blood examination showed nothing abnormal, we proceeded to find how the boy could handle a heavy carbohydrate meal, 75 gm. of glucose (to an adult 100 gm. are given) in lemonade.

The glucose tolerance curve (Curve 1) shows a very gradual rise, its highest point being reached at the end of three hours, and just the beginning of descent at the end of four hours, so that were we to project this curve we would find that it would take from seven to nine hours for it to return to the starting point. In this case, therefore, a typical diabetic curve was secured. The glycosuria did not appear until the blood-sugar content had reached 272 mg. per 100 cc, showing that the point of kidney permeability to sugar lay somewhere between 84 and 272 mg. per 100 cc.

Thus, while we were not able to make any definite diagnosis in this case before the tolerance test was made, following that test we were able to say with confidence that it was a diabetic case, basing this conclusion on the proved lack of carbohydrate utilization. If even more definite evidence is desired, it can be secured by letting such a case go on for a few months on an unrestricted diet, when the typical picture of severe diabetes will develop and special diagnostic measures will not then be needed to confirm the diagnosis.

This boy was put on a gradually increasing diet, checked by repeated blood-sugar examinations so that today, after a two weeks' stay in the hospital, I am discharging him on a diet of 45 gm. of carbohydrate, 55 gm. of protein, and a total of 1700 calories on which his blood sugar remains normal, his last examination showing 73 mg. per 100 cc; no acetone.

This case illustrates not only the procedure whereby the diagnosis of diabetes is established, but also the importance of immediately and relentlessly pursuing the treatment, for especially in children, there is no time to lose. To my mind, diabetes and diphtheria in children have one point in common—they must be treated with promptness if we would get results. There is a critical period in diphtheria beyond which serum is of no avail; there is a critical period in diabetes in children beyond which treatment is of little or no avail. We know only too well the story of cases of advanced diabetes in children.

CASE II.—A young foreign girl, aged twenty-six years, a housemaid, came in after following a diabetic regimen for three weeks. She had begun to feel that this was too difficult and wanted a confirmation of the diagnosis.

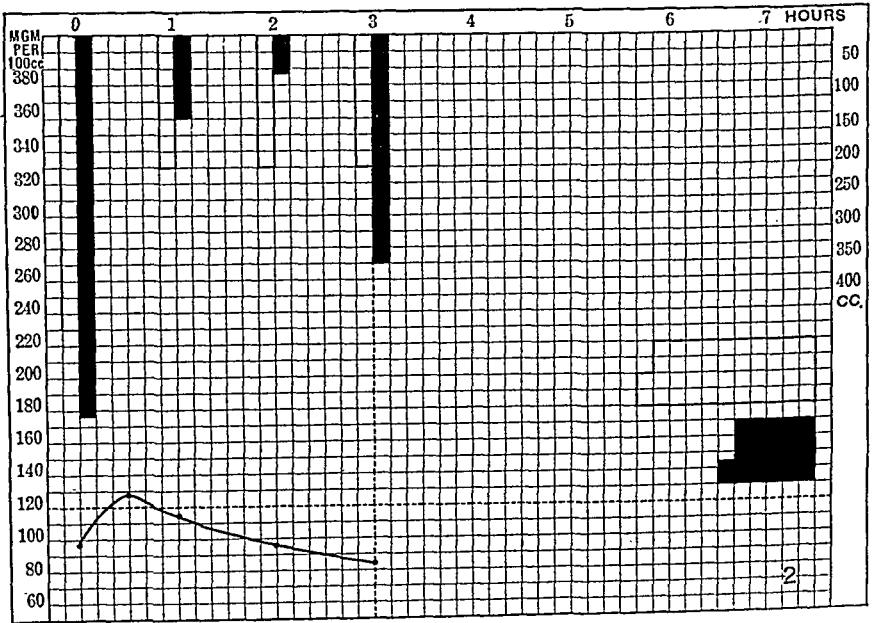
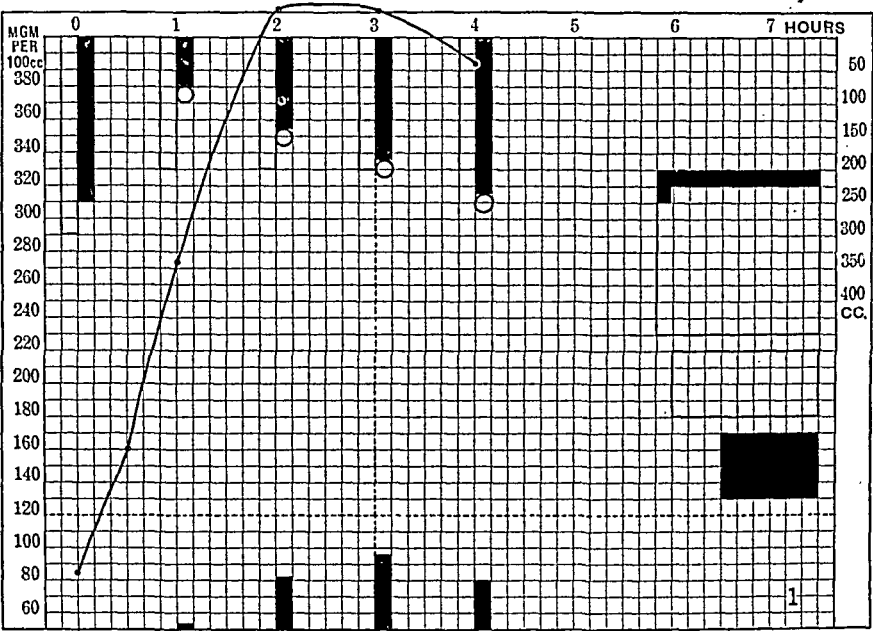
Her family history was of no significance. She had had measles in childhood, influenza four years ago. Her physical examination showed nothing abnormal; blood-pressure, 120-80. There was no sugar in the urine. The fasting blood sugar was 111 mg. per 100 cc; urea, 42 mg.; Wassermann, negative.

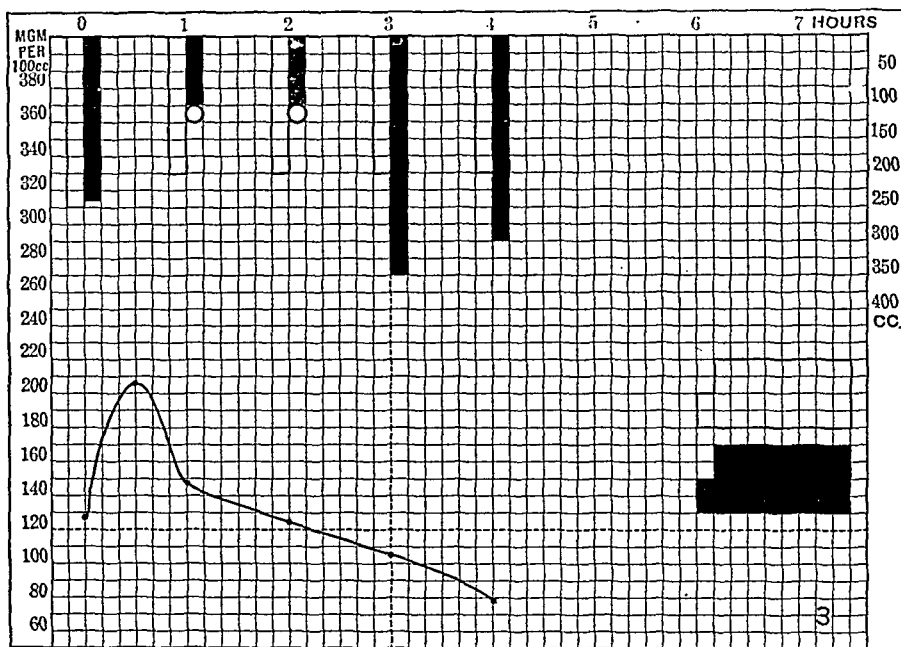
In this, as in the preceding case, there were no pathological findings, nothing upon which to base a definite diagnosis of diabetes and substantiate the primary diagnosis of the family physician. On the other hand the previous diagnosis could not be disproved on the basis of this examination, for it might be that the normal blood-sugar content was the result of the restricted diet as in the case reported above.

The results of the glucose tolerance test as shown in Curve 2 disclosed a perfectly normal carbohydrate tolerance, in fact a strong carbohydrate tolerance, proving that this was not a case of diabetes.

One cannot question that sugar had been found in the urine; it might have been a postprandial event. But to base the diagnosis

of diabetes on one urinary examination, and to stop there means subjecting the patient to a hard antidiabetic regimen which is not justifiable unless the diagnosis is confirmed.





The checkered columns at the top of the charts indicate the water intake; the solid black columns at the top indicate the urine output. The total intake and output during the period of four hours or more is indicated by a like marking at the lower right corner of the chart. The dots at the lower ends of the black columns indicate the presence of sugar in the urine.

The broken horizontal line opposite "120" is the normal level of blood sugar, *i. e.*, 120 mg. per 100 cc. The broken vertical line opposite "three hours" indicates the period within which, in normal individuals, the blood-sugar content again becomes normal after the ingestion of the standard dose of glucose. The heavy curve represents the blood-sugar content at the designated periods. The dots which break the glucose tolerance curve indicate the intervals at which blood was taken for sugar estimation. Each solid black column at the bottom of the charts represents the sugar content of the urine output indicated by the corresponding solid black column at the top of the chart. Each square included in these lower columns represents 1 gm. of sugar, and the total sugar output, the sum of these squares, is indicated by the solid black portion of the large square at the right of the chart, which includes 100 squares, representing 100 gm. of glucose, the total sugar intake.

**CASE III.**—A plumber, aged thirty-four years, Jewish, married, came in for a consultation regarding a diagnosis of diabetes which had been made nearly two years before when sugar was found in his urine in an examination for life insurance. He was then referred to an internist who made a blood-sugar examination, with a normal finding, and then made a glucose tolerance test, which showed fasting blood sugar 110 mg. per 100 cc; one-half hour after the glucose ingestion, 193 mg.; one hour after, 200 mg.; two hours after, 158 mg., when the test was discontinued. There was no sugar in the urine at the beginning; 1.3 per cent at the end of one hour; 3.4 per cent at the end of two hours. On this finding, the diagnosis of diabetes was again made and the man was kept on a diabetic regimen for two years.

I made a glucose tolerance estimation at the end of this time, the results of which are shown in Curve 3. This is a normal tolerance curve and is almost a duplicate of the curve made from the findings two years ago. There was no glycosuria to start with, but it was present at the end of the first and second hours.

This curve made it possible for me to tell the man definitely that he was not a diabetic, in spite of the fact that he had been so diagnosed by two physicians and belonged to the race which has a strong predilection for diabetes.

In order to confirm the diagnosis beyond the shadow of a doubt, I subjected the patient to forced carbohydrate feeding, explaining to him that I was doing this in order to overtax his carbohydrate metabolism so that at the end of the week, if there were a deficiency, it would be manifested by a high blood-sugar content; if there were no deficiency, then the blood sugar would be normal.

The patient agreed, and for a week he feasted on pastry and cakes and all the carbohydrate food he could think of, for which he had longed for nearly two years. At the end of this time he showed a fasting blood-sugar content of 102 mg. per 100 cc. This certainly was sufficient evidence for considering the case to be a non-diabetic. For over a year his diet has been unrestricted and his blood sugar has been normal at each examination. The last examination showed a blood sugar content of 111 mg. per 100 cc.

**Conclusion.** The various case histories cited above emphasize the following important point in the diagnosis of diabetes:

If one bases his diagnosis on urinary examination alone there may result on the one hand danger to the patient if diabetes is present, and on the other, disadvantage and misery from a deficient diet, if the patient is not a diabetic; in the case of a mistaken insurance examination, not only the patient but his family also may suffer an injustice.

## REVIEWS.

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EPISCOPAL HOSPITAL REPORTS. Volume V. Pp. 506. Philadelphia: William J. Dornan.

THIS is a volume of splendid appearance and is well edited. About twenty-two members of a staff of fifty-seven act as contributors, together with about ten resident physicians. Most of the reports come from the surgical side of the institution with the name of the editor, Ashhurst, attached to twenty papers, about one-third of the volume. There is a lamentable lack of material from the medical staff. Most of the papers have appeared in some medical publications and are for the most part case reports. It is to be regretted that so active an institution as the Episcopal Hospital has had so little to offer. Perhaps the period of the war may be an excuse. The institution has a publication fund made possible by the contributions of a generous friend. It is to be hoped that the next report contains papers showing more of a research spirit.

S.

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THE COLLOIDAL STATE IN ITS MEDICAL AND PHYSIOLOGICAL ASPECTS  
By SIR WILLIAM M. BAYLISS, F.R.S., M.A., D.Sc., LL.D.,  
Professor of General Physiology in University College, London.  
Pp. 95; 12 figures. London: Henry Frowde, Hodder & Stoughton, 1923.

THIS monograph is to be regarded as an attempt to give a short account of the properties of colloids, so far as of interest in connection with the phenomena occurring in living beings. The nine chapters discuss; (1) the nature of the colloidal state; (2) interfacial phenomena; (3) precipitation and peptonization; (4) osmotic pressure; (5) viscosity; (6) surface tension of colloidal solutions; (7) imbibition; (8) physiological action; (9) proteins and hemoglobin. Although the form of the booklet necessitates rigorous selection of topics, the author finds space to explain his individual views on the colloidal state and to express his disagreement with Jacques Loeb on more than one detail. To the rapidly growing group of medical men who feel the need of greater familiarity with adsorption, the



isoelectric point, amphoteric electrolytes, the Donnan equilibrium and kindred topics, this timely and relatively simple presentation by a master of the subject will be most welcome. K.

UEBER DIE PATHOLOGISCHE ANATOMIE DER SPIROCHÆTOSIS ICTERO—HÆMORRHAGICA INADA (WEILSCHE KRANKHEIT). By PROF. DR. RENJIRO KANEKO, a.o. Professor I. med. Klinik der Kyushu Imperial Universität, Japan. Pp. 182; 12 illustrations and numerous tables. Vienna: Rikola Verlag, 1922.

A THOROUGH systematized inquiry into the morbid anatomy of the Japanese form of this disease, written in the manner of the previous generation, now unfortunately rare, and based on eight years personal observations of cases, of which 42 had come to autopsy. Coupled with a fifty page critical review of the literature, this book is a valuable contribution to the subject; though the reader must remember that the European form of the disease is not identical and that still another epidemic jaundice has recently been shown to exist in this country. K.

THE PRACTICE OF MEDICINE IN THE TROPICS. Volume III. By many authorities. Edited by W. BYAM, O.B.E., Lieut.-Colonel, Royal Army Medical Corps (retired); Lecturer on Tropical Medicine at St. George's Hospital Medical School; late Assistant Director of Pathology, London District; and R. B. ARCHIBALD, D.S.O., M.D., Edinburgh; Major, Royal Army Medical Corps (retired); Director of the Wellcome Tropical Research Laboratories, Soudan Government, Gordon College, Khartoum. Pp. 865; 32 illustrations. London: Oxford Medical Publications, 1923.

THE third volume of Byam and Archibald's practice of tropical medicine is preceded by a very splendid likeness of the late General Gorgas, a particularly appropriate and a very agreeable courtesy from our English colleagues. This volume takes up in detail the diseases produced by intestinal parasites, diseases caused by physical agents, diseases of doubtful causation, some of which are present in the temperate climate, as for example rabies and smallpox. These sections are then followed by disorders of metabolism as seen in the tropics including the deficiency diseases. Regional diseases are considered in another section, a section on surgery in the tropics and a rather unusual section on diseases of women in the tropics.

The sections, as in the previous two volumes, are extremely complete and very thorough, and are presented by well-known authorities. It is interesting to note the opinion of the authors as to the etiology of some of the disorders which are at present in question. Pellagra is considered to be the result of a possible inherited predisposition with continued dietetic deficiency. Typhus fever is classified in the doubtful diseases and possibly, although the authors of the section on typhus fever do not believe it, due to the *Rickettsia protazeki*. The same thing holds good for Rocky Mountain spotted fever and trench fever. The last two diseases are probably due to the *Rickettsia* bodies.

The third volume completes this monumental work in tropical diseases and undoubtedly this present publication will stand for many years as the recognized authority on these various manifestations of disease which are observed chiefly in the tropics. M.

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THE BACTERIOPHAGE—ITS ROLE IN IMMUNITY. By F. D'HERELLE, Pasteur Institute. Authorized English Translation by GEORGE H. SMITH, Assistant Professor of Bacteriology, Yale University. First edition. Pp. 282; 14 illustrations. Baltimore: Williams and Wilkins Company, 1923.

THE book consists of two parts. Part I deals with the methods of isolation and the demonstration of the Bacteriophage. Part II discusses its importance in disease and its role in immunity. D'Herelle gives the student the benefit of his extensive researches. His conclusions as to the nature, the role in disease and immunity are often at variance with those of other investigators; however the author takes great pains in answering criticism, in an effort to prove his theories. The problem is one of great experimental interest, but the author is undoubtedly overestimating its ultimate value.

P.

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ENVIRONMENT AND RESISTANCE IN TUBERCULOSIS. By ALLEN K. KRAUSE, A.M., M.D., Associate Professor in Medicine, Johns Hopkins University; Director, Dows Tuberculosis Research Fund, Johns Hopkins University; Editor, American Review of Tuberculosis. Pp. 137. Baltimore: Williams and Wilkins Company, 1923.

THESE two essays by an author of recognized authority will interest those seeking more light upon the mechanism of resistance to tuberculosis. The formation of the tubercle, its chance position,

its age and vascular supply, the part played by trauma, strain, intercurrent infections, and finally allergy, are all discussed in a masterly fashion. A.

MASSAGE AND MEDICAL GYMNASTICS. By DR. EMIL A. G. KLEEN. Second edition. Pp. 564; 182 illustrations. New York City: William Wood & Co.

THIS book of Dr. Kleen's has been a guide for doctors, medical students, masseurs and medical gymnasts in Scandinavia for more than a quarter of a century. The original edition appeared over twenty years ago and so well satisfied has the author been with its original contents that he has found no reason for making any material alteration in the present edition. The present volume contains a chapter on Ling's Medical Gymnastics by Dr. J. Arvedson, a chapter by Dr. E. Zander on Zander's Medical Gymnastics and another chapter by Dr. Patrik Haglund on the use of Medical Gymnastics and Massage in Orthopedics.

This book, coming as it does from Sweden, where methods of massage and gymnastics have received scientific thought for the last hundred years, makes it a book well worth investigation for those who are laboring in this field. It includes a most interesting historical introduction which goes to show that massage and physical exercise have formed a branch in medical and surgical treatment from time immemorial in all countries. Naturally, some of the authors views receive criticism when read by English-speaking people. This does, by no means, minimize the value of the book. The illustrations are somewhat antiquated, although they serve the purpose quite satisfactorily. The important thing in the reviewer's mind concerning such a book as this one, is that it calls increasing attention to the value of physical methods of treatment. The need for such a knowledge was demonstrated anew in the work of recent war surgery. There is no doubt that too little attention is paid to this branch of therapeutics by the average medical curriculum. S.

FOOD AND THE PRINCIPLES OF DIETETICS. By ROBERT HUTCHINSON, M.D., EDIN., F.R.C.P., Physician to the London Hospital, and to the Hospital for Sick Children, Great Ormond Street. Fifth edition. Pp. 610; 33 diagrams and 3 plates. New York: William Wood & Co., 1922.

THIS is an ably written and rather comprehensive text-book, the original edition of which appeared in 1900. While obviously some

attempt has been made to bring the present edition abreast of the times the impression one gets in reviewing it is that it represents in the main the state of knowledge of dietetics a decade or two ago. Many of the references, and they are quite profuse for a book of this kind, date back into the Nineteenth Century and the food prices quoted are those of prewar days. In spite of this defect the work is a most satisfying one, presenting the principles of dietetics in a rational and most convincing manner, and a careful perusal of it will repay anyone.

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M.

CANCER AND ITS NON-SURGICAL TREATMENT. By L. DUNCAN BULKLEY, A.M., M.D., Senior Physician to the New York Skin and Cancer Hospital, Member of the American Association for Cancer Research. Pp. 457. New York: William Wood & Co.

THE surgical aspects of cancer have so monopolized the clinical literature on cancer in recent years that it is very refreshing to come across a book that deals solely with the medical features. Bulkley has aimed, as he states in the preface, to establish on firm scientific grounds the proofs of the constitutional nature of the disease and to illustrate the value of this thesis by cases, in many of which he has obtained quite remarkable results by purely medical treatment. He does not believe in the local nature of the affection, looking upon the tumor itself merely as a manifestation of a general disease, carcinosis. In his analysis of known clinical and experimental facts he presents a strong case for his theory, which after all is not new though much neglected of late.

M.

ABDOMINAL PAIN. By PROF. DR. NORBERT ORTNER, Chief of the Second Medical Clinic at the University of Vienna, Authorized Translation by WILLIAM A. BRAMS, M.D., Formerly Lieutenant-Commander, Medical Corps, U. S. N., and DR. ALFRED P. LUGER, First Assistant, Second Medical Clinic, University of Vienna. Pp. 362. New York: Rebman Company, 1922.

THIS is an English translation of the second and latest edition of Ortner's well known work on Abdominal Pain. In the author's preface to this American edition he expresses the hope that it will be a means of helping in reestablishing friendly relations between members of the medical profession of the English-speaking countries and of his own. It is very evident that he has in mind the propaganda for the restoration of Vienna to its prewar status as a post-

graduate medical center. The war has undoubtedly demonstrated for us, at least, that American centers afford just as good opportunities for study and that the European doctor is in no respect our superior. Medicine should, of course, know no nationality, but it is rather difficult to forget the attitude taken by some of the central power scientists prior to and during the war.

The present edition is arranged much as was the previous German edition and takes up the subject from every angle. Diffuse and localized abdominal pain, epigastralgia or stomach cramps, pains in all of the abdominal regions and pains associated with various phenomena are taken up in the different chapter headings. In the lines of the book, the author sets forth his own wide personal experience, one based upon the verification of clinical observation by surgical and anatomical check-up.

The impression that one quickly receives in reading the book is that its author has a profound and extensive insight into his field. Often one wishes that he had not been so concise. The effect is much as though one were seeing a country from a swiftly moving express train.

Somehow or other the style fails to drive home the subject-matter. The topic of abdominal pain is, of course, a large, difficult and intricate one to handle and we know of no one who has presented the case in a better way. Perhaps the fact that we are dealing with a translation accounts for some of our objections.

As for the facts as they are thrown on the screen, no objection could be made against them. We were interested in the terms liver colic, hysterical fever and the evident importance attached to the Abderhalden reaction in pregnancy. The book deserves the attention of all who may be interested in medicine and more particularly internal medicine. It has much of value crowded between its covers.

S.

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THE SPECTROSCOPE AND ITS USES IN GENERAL ANALYTICAL CHEMISTRY. By. T. THORNE BAKER, A.M.I.E.E., F.R.P.S. (author of Radiographic Technic). Second edition. Pp. 208; 98 illustrations. New York: William Wood & Co., 1923.

THIS small book, which first appeared in 1907, was written to fill an intermediate position between the ordinary text-book of physics and advanced works on the spectroscope. Of the ten chapters into which it is divided the medical man will find the first three the most useful. Such subjects as spectrophotography and spectrophotometry, fluorescence, phosphorescence and caloriscence are taken up in the later chapters, with a final one on roentgen-ray spectral analysis.

K.

CONTRIBUTION A L'ÉTUDE DES MANIFESTATIONS TARDIVES DE L'ENCÉPHALITE EPIDÉMIQUE. By GABRIELLE LÉVY (Service du Professeur Pierre Marie). Pp. 312; 57 illustrations: Paris: Vigot Frères, 1922.

THIS book is the result of intensive study of 129 cases in the clinic of Professor Marie of the results that may follow an acute attack of epidemic encephalitis. It is well brought out that the severity of the acute symptoms bear no relation to the results that may follow. The sequelæ in the order of their importance are: (1) The Parkinsonian syndrome (which the author very carefully differentiates from Parkinson's disease); (2) the excitomotor syndrome, including the choreas and all other types of involuntary movements; (3) the insomnia and hypomanic forms which occur especially in children; (4) the respiratory form. The histories of 68 cases are given in detail. The pathology of 4 cases is gone into and the literature reviewed. In 1 case there was a persistence of the acute changes which is interpreted as pointing to the virus persisting. It is a very readable book and is an important contribution to our knowledge of what may happen to a patient who recovers from acute epidemic encephalitis. W.

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THE SUCCESSFUL PHYSICIAN. By VERLIN C. THOMAS, M.D., Visiting Physician to Franklin Hospital, San Francisco. Pp. 303. Philadelphia and London: W. B. Saunders Company, 1923.

To those physicians who believe that their success depends primarily upon the amount of money they accumulate, this book will greatly appeal, for it discusses the various aspects of their life from that angle. This includes methods of attracting and holding patients, of becoming favorably known in one's community and of changing ability into income. The book also includes chapters on personality, choice of location, forms of practice, accounts, investments, insurance, etc. The opinion is expressed by the author that young men go into this profession essentially for selfish reasons and only incidentally for altruistic ones. And furthermore the author admits that but few doctors are able to put aside enough money for their comfort in old age. The logical conclusion is that physicians are not usually successes. This conclusion is obviously a false one and in itself disproves the author's standard of success. Scattered through the book are some helpful suggestions for the beginner in practice, but much of the advice given is not needed by the graduate of today, and the emphasis placed on material success is unfortunate.

M.

ORTHOPEDIC SURGERY. By SIR ROBERT JONES, K.B.E., C.B., and ROBERT W. LOVETT, M.D., F.A.C.S. Pp. 699; 712 illustrations. New York: William Wood & Co., 1923.

THE hopes aroused by the names of the eminent authors are fully justified by the book. The ever-widening field of orthopedic surgery is exemplified by the range of its contents, which includes almost all diseases of the locomotor apparatus, whether of bone, joint or nerves, except the acute infections and recent fractures. A valuable feature of the book is the introductory remarks on anatomy, functions and general pathology of the parts under consideration, which seek to correlate symptomatology and treatment with general principles of disease and disordered function rather than with each separate entity. This not only aids the memory but helps the student and practitioner to formulate treatment on a rational basis. The book excels in the presentation of those subjects which have long been regarded as the special field of orthopedic surgery, *e. g.*, tuberculosis of the bones and joints, congenital deformities, static and other acquired deformities and principles and details of apparatus, muscle-training, etc. The subjects of bone tumors and malunited fractures are treated less comprehensively, but this can scarcely be regarded as a defect.

Typography, paper and illustrations are excellent. This book is certainly the standard single volume work on orthopedic surgery in the English language. P.

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ARAB MEDICINE AND SURGERY; A STUDY OF THE HEALING ART IN ALGERIA. By M. W. HILTON-SIMPSON, B.Sc. (author of *Among the Hill Folk of Algeria*, etc.). Pp. 96; 12 illustrations and 8 plates. London: Oxford University Press, Humphrey Milford, 1922.

OWING to the kindly interest taken in his work by the late Sir William Osler, the author, himself a layman, presents certain very interesting data regarding the present-day medicine and surgery of the practitioners of the remote valleys of the Aures Mountains. He and his wife spent four winters there making an ethnographical survey and were able to get into very close touch with many of the native doctors, learning from them many of their professional secrets. These are presented from the point of view of the native physician and make very entertaining reading. It is exceedingly enlightening to realize that even today, in a French colony, trephining operations are frequently performed with crude red-hot instruments on patients without anesthesia, and that fever is treated by magical observances. M.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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**Further Observations on the Roentgen-ray Treatment of Toxic Goiter.**—MEANS and HOLMES (*Arch. Int. Med.*, 1923, 31, 303) start their article by making an announcement of the fact that this is a continuation of some earlier work published in 1917 and again in 1919. The new cases include 44 cases of exophthalmic goiter and 14 cases of toxic adenoma. Later, they plan to report on the cases treated by surgery alone or by surgery and roentgen-ray combined. In the introduction they give the credit to F. H. Williams for first using the rays in exophthalmic goiter. The use of it rapidly spread so that in 1908, Pfahler and Zulick reported upon a large number of cases. At the Massachusetts General Hospital they have a special thyroid clinic and representatives of the medical, surgical and roentgen-ray staff. Each new case is gone over thoroughly by each representative of the special staff. The method of treatment consists of the following details: Acting upon the principle that the effect of radiation will be the greater the larger the amount of radiation absorbed and the more active and less stable the cells composing the gland at the time of exposure, they attempt to obtain the largest possible dose possible without injury to the skin. In general, they find that a reduction of at least 25 per cent of the calculated dose is necessary if reddening and tanning are to be avoided, thus obviating the dangers of atrophy and telangiectasis. They give the treatment approximately every three weeks, but do not continue treatment past a period of five months. Three areas are exposed: One on each side of the neck or thyroid and one over the upper part of the sternum in the region of the thymus. In their recent series of *exophthalmic goiter*, 44 patients in all, 16 showed little or no improvement, 8 of these came to operation later and were



apparently cured. Of the 28 patients listed as improved, 12 were cured and 16 were improved, but were not rendered free from hyperthyroidism. No case seemed to be made worse by the treatment. Two patients that were improved but not cured were later operated upon and 1 of these died. They then illustrate their article with a protocol of every case with a series of illustrative charts, showing how there is usually a decided fall in pulse, basal metabolism and an increase in body weight after roentgen therapy. Five cases with *toxic adenoma* were cured out of 14. They also report on 9 of the 15 patients treated by roentgen-ray previous to 1919. Of the remaining 6, 3 have been lost and 3 have died. Six of the 9 patients have normal metabolic rates five or six years after their first treatment; 1 has a slight elevation without clinical signs. The remaining 2 have elevated metabolism, and clinically were better but not well. They then take up the questions of whether the roentgen-ray itself did any good in toxic goiter, whether it works in all cases, what the manner of its action is and the permanency of the effect. They believe that the roentgen-ray has a decided effect. They discuss Plummer's contention that the natural course of exophthalmic goiter is an uneven one: The patient may get well without treatment. Plummer criticized their previous reports on lack of control patients, and they discuss this and use as an analogy the dietetic treatment of peptic ulcer. Concerning the question of what evidence we have that roentgen-ray is an agent capable of inhibiting or destroying cell function, it has been shown by laboratory investigations that if a living organism be exposed to radiation, retardation of growth, inhibition of function and death to the organism will take place, and that this change will be dependent upon the amount of radiation absorbed, the character of the cells rayed and the conditions to which they are subjected before and after radiation. They also bring out the point that glandular functions are especially sensitive to radiation. About one-fifth of a dose necessary to produce slight reddening of the skin if absorbed by the ovaries will cause cessation of the menses. Similar doses will stop the flow of spermatozoa from the seminal fluid, and a much smaller dose will stop the flow of saliva from the parotid gland. As far as the thyroid goes, it is possible to produce myxedema by the use of the rays. They believe also that in about two-thirds of the cases vigorous roentgen-ray treatment is followed by progressive improvement shown by clinical signs, by behavior of the pulse, metabolism and body weight. This continues for about four or five months and may go on to recovery or may fall short of it. When the latter takes place the treatment seems of little value. In cases that have shown marked improvement and have then relapsed a second course of treatment is indicated. Patients who do not respond to the roentgen-rays in four or five months and those who while improved are not cured should be given the benefit of surgery. They contend that the proper way of using the roentgen-ray in exophthalmic goiter is to give it a fair trial with the idea it may effect a cure, or if it does not, it makes the patient a better operative risk by reducing the degree of hyperthyroidism. In answer to the question why roentgen-ray should be used instead of operation, they say that in operation there is always a certain mortality. Neither method is an ideal method of treatment

and neither attack the cause of the disease. In the matter of toxic adenoma here surgery is decidedly indicated, because the seat of trouble is in the thyroid, and surgery removes the cause, although roentgen-ray gives very decided improvement. The authors discuss the effect of rest also in the treatment of these cases and the removal of focal infection, also the course of pregnancy and cardiac complications. Their conclusions in brief are that roentgen-ray is beneficial in toxic goiters; two thirds of the patients improve; the patients make better operative risks.

**Vaccination of Monkeys against Pneumococcus Type I Pneumonia by Means of Intratracheal Injections of Pneumococcus Type I Vaccine.**

—CECIL and STEPHAN (*Pub. Health Reps.*, Washington, 1922, Reprint 796) have previously attempted to immunize troops against Type I pneumococcus infections by subcutaneous administration of killed pneumococci. In the present paper they report the results of experimental observations on monkeys which they attempted to immunize actively by intratracheal injections and inhalations of killed pneumococci Type I. Striking success followed the intratracheal injections, and this was obtained with smaller doses (one-tenth) than when subcutaneous administration was used. Pneumococcus spray, when inhaled, failed to induce immunity. This is possibly explained by subsequent experiments with India ink which showed that monkeys would allow little or none of the vaporized fluid to enter the trachea, a difficulty which would not be encountered in vaccinating man by the spray method. The authors believe that immunity established by intratracheal injections of pneumococcus vaccine is cellular in character. Little or no protective substance can be demonstrated in the serum of monkeys vaccinated by this method.

**Observations on the Role of Cockroaches in Disease.**—McFIE (*Ann. Trop. Med. and Parasitol.*, 1922, 16, 441) in his opening paragraph, remarks, "As the cause of disease and as possible carriers of pathogenic organisms, cockroaches have received less attention than other domestic pests, and less than might have been expected, considering their wide distribution, their abundance especially in tropical countries, their filthy habits and the opportunities they have of contaminating food, and the almost universal loathing with which they are regarded." The author's studies showed that the following organisms appeared to pass unharmed through the intestine of the cockroach (*Periplaneta americana*): *B. tuberculosis*, *B. lepræ*, cysts of *Entameba histolytica*, *E. coli* and of an ameba of a monkey resembling *E. coli*, cysts of *Giardia intestinalis* and eggs of *Ankylostoma duodenale*, *A. braziliense*, *Necator americanus*, *Ascaris lumbricoides*, *Trichuris trichiura*, *Tenia saginata* and *Schistosoma hematobium*. On the other hand, gonococci, the vegetative forms of *Entameba histolytica*, *E. coli*, eggs of *Aphiocheta xanthina*, and in two experiments each, *Bacillus typhosus*, *B. paratyphosus* and *B. dysenteriae* (Flexner Y) were not recovered from the feces of cockroaches after experimental feeding. No evidence was obtained that any of the organisms used in the experiments established themselves as parasites in the intestine of the cockroaches.

## SURGERY

UNDER THE CHARGE OF

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**Ptoxis of Right Colon.**—QUAIN (*Arch. Surg.*, 1923, 6, 638) says that coloptosis is a very common anatomic abnormality. Comparatively few of those who have a ptotic colon suffer serious symptoms. Some of the effects of coloptosis are translated to other abdominal organs, which may then give rise to a new set of symptoms, thus obscuring the original and chief cause of the trouble. Medical treatment gives relief in most cases and should be given a thorough trial in all cases, but its ability to cure is doubtful in any case. Surgical treatment is as successful in these lesions as in many other so-called surgical diseases and promises better results as experience accumulates. Chronic appendicitis is an infrequent disease and the term should be restricted to those comparatively few instances in which there actually is a chronic lesion of the appendix.

**Spondylolisthesis.**—KLEINBERG (*Ann. Surg.*, 1923, 77, 49) says that the condition occurs more frequently in males than has been believed heretofore, especially among laborers. Trauma is frequently the direct cause or at least a very important factor in etiology. There is a definite radiographic appearance which is pathognomonic and has not been found or described for any other lesion. The last lumbar is larger than the other vertebrae. The main feature of roentgenogram in the lumbosacral region is the distinct outlining of each lumbar vertebra with the fifth, separated from the sacrum by a definite interval. Therefore, when the superior surface of the last lumbar vertebra is seen while the other vertebrae appear quadrilateral, then a diagnosis of forward dislocation of the last lumbar vertebra is justifiable, while in a clear lateral view the presence of the shadow of the body of the last lumbar in front of instead of above the sacrum makes the diagnosis absolutely positive. This lateral finding is of prime importance.

**The Metastasizing Tendency of Esophagus Carcinoma.**—HELSLEY (*Ann. Surg.*, 1923, 77, 272) says that in 70 per cent of carcinoma of the esophagus, metastases were present in 36 per cent. In 6 per cent the secondary growths were limited to the regional lymph nodes. This indicates a limited tendency to metastasize. The average duration of symptoms, 4.8 months in the patients who died without metastases, indicates that in the majority of cases ample time is given for diagnosis and treatment before metastases occur. However, the striking change for the worse in the pathological picture during the average of sixty-

nine days by which the group that survived gastrostomy outlived the group that succumbed thereto gives warning of the speed with which metastases developed in a somewhat advanced stage of the disease. Irrespective of the duration of the disease, the possibility of metastasis formation without definite evidence of the same should not be considered as a contraindication to radical operation.

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**Primary Carcinoma of Liver.**—HELVESTINE (*Jour. Cancer Res.*, 1923, 7, 209) says primary carcinoma of liver occurs in 0.03 per cent of all necropsies, according to statistics collected by Winternitz. It therefore occurs very rarely in the experience of any single pathologist. The condition is rapidly fatal, for the duration of the disease seldom exceeds three months. Despite its malignancy surgical intervention has met with some success. One author has reported reoperation for recurrence seven years after removal of primary growth. Hepatomata are differentiated from cholangiomata by the arrangement of the cells, the presence of capillary stroma and the absence of proliferation of the bile duct epithelium. Cirrhosis was not present in the case analyzed. The growth was unicentric in origin, the primary focus being in the right lobe, whence it grew by direct extension without using the portal system as a pathway.

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**Stoffel Operation for Spastic Paralysis.**—HEYMAN (*Surg., Gynec. and Obst.*, 1923, 36, 613) says that from the results obtained by the Stoffel operation in a series of 24 cases the spastic contractures of the adductors and spastic equinus can be absolutely relieved. Only 2 cases of contracture of hamstrings were operated and the evidence is not sufficient for opinion. In one of these, however, recurrence had followed tenotomies, and at present writing, one year after the Stoffel operation, there is no tendency toward contracture; while spastic contracture of the fingers and thumb can be relieved, the ultimate function of the hand is not so encouraging as in the lower extremity. The author believes that the results are due to the extreme complexity of motions acquired in the normal hand.

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**Renal Function Following Nephrotomy.**—MAGOUN (*Surg., Gynec. and Obst.*, 1923, 36, 675) says that the arrangement of the arteries of the kidney differ in man and dog. Complete nephrotomy bilateral or unilateral may be performed in dogs with maintenance of life and renal function. A single kidney may be subjected to nephrolithotomy and maintain sufficient function to support life and health. Secondary hemorrhage is a real danger in complete section of the kidney. Smaller incisions, single or multiple, may be made into the kidney, to remove stone with small risk of secondary bleeding. Generally, pelviotomy is the operation of choice in the treatment of renal calculi. However, in selected cases nephrolithotomy is indicated.

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**The Conservation of Muscles in Paralytic Deformities of the Foot.**—ROBERTS (*Jour. Bone and Joint Surg.*, 1923, 5, 123) says that no single muscle of a group supplied by the same terminal nerve is likely to be paralyzed if the other members of the group have regained nearly normal power. Working on this observation the author has devised

very satisfactory treatment in types of valgus deformity in which the tibialis anticus is functionless and in the movement of dorsiflexion the foot is drawn outward by the action of the common extensor in spite of vigorous effort on the part of the extensor hallucis to maintain the median position. The tibialis anticus is apparently paralyzed with the other two of the group supplied by the deep peroneal nerve functioning well. The author suggests the inability of the tibialis anticus to function is due to stretching and the consequent atrophy from disuse. The operative procedure consists essentially of reinforcement of the tibialis anticus. Sixty-six cases so treated show definite return of contractility in the tibialis anticus muscle three months after the splints had been removed.

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**The Mercury Inhalation Therapy of Syphilis.**—GUTMAN (*Am. Jour. Syph.*, 1923, 7, 145) says that mercury vapor inhalation therapy has been employed very extensively in many countries and for many centuries, that numerous competent physicians in almost all countries and almost all times utilized this therapeutic factor in the cure of syphilis and other diseases. Mercurial vapors when administered in sufficient quantities have never lacked action, always producing results, either desirable or undesirable. Pure metallic mercury was rarely used, but the drug was commonly employed either impure or in chemical combination. Complications are noted most frequently when other substances have been added to the mercurial compounds. Older physicians for one reason or other mixed the mercurial substance with foreign, mostly undesirable ingredients. The vaporization process of mercury mixtures was conducted in a multitude of ways, while the vapor was administered in an indiscriminate manner, and while there is much in the past history of mercury vapor therapy that is unfavorable, there is much more which commends the method and places it among other recognized procedures.

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**Coxa Plana and its Causation.**—JANSEN (*Jour. Bone and Joint Surg.*, 1923, 5, 265) says that the femoral head and neck, when being deformed to the condition which was first described by Dr. Tagg, passes through several flattening stages, with some fragmentation of its bone center. This final stage is called coxa plana fragmentation. On further growth these fragments reunite to form a wide femoral head in the adult. It is well known that coxa plana is a satellite of congenital dislocation of the hip and reversely. Patients with coxa plana are regularly distinguished from those with *bacterial* inflammations by their healthy appearance, the small amount of pain, the absence of fever and mostly by the absence of reflex stiffness and restriction of movement throughout life. Bacteria cannot explain the thickness of the socket floor or the ischium varum, the horizontal position of the growth disk and the correlation with congenital dislocation of the hip.

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**Tendon Transplantations for Musculospiral Paralysis.**—STEVENSON (*Glasgow Med. Jour.*, 1923, 17, 225) says that musculospiral paralysis is a comparatively uncommon occurrence in surgical wards of a general hospital, usually occurring with fractures of the upper arm or accidentally during an operation. The author has noted that a clean cut of

the musculospiral which was immediately sutured was followed by a period of inactivity for one year before restoration of voluntary movement in extensor muscles; the alternative operation is tendon transplantation. The technic is described by the author, modifying Stile's original operation. The procedure is constant regarding three tendons. The entire flexor carpi ulnaris is used as the transplant for the extensor communis digitorum, extensor indicis and minimi digiti. Palmarislongus if present is inserted into the radial extensors. Reëducation of the transplanted muscles is invaluable in this stage. Wrist flexion is continued satisfactorily by the action of the flexores sublimis and profundus digitorum.

## THERAPEUTICS

UNDER THE CHARGE OF

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AND

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**Ionic Medication.**—The theory of ionic medication was originally enunciated by Verratti in 1747 and was introduced into therapeutics by Leduc in 1900. The enthusiasm of the proponents of this method of treatment and the vehement condemnation of its opponents led CAMPBELL (*Brit. Med. Jour.*, 1923, 1, 409) to undertake a critical examination of the whole subject. He concludes, from a considerable number of experiments and clinical observations, that (1) the amount of any drug (iodine, strychnine, pilocarpine, atropine, salicylate) that can be introduced in an ionic state into the body by electric currents which can be used therapeutically is very small. (2) The drug, as soon as it is carried through the skin, is swept away in the blood stream and produces its usual specific effects on the system generally. There is no local concentration. (3) There is no evidence of deep penetration; all the evidence is against the drug's penetrating farther than the subcutaneous tissue. (4) There is no evidence in support of the claim that in the process of ionization chemical changes are set up in the tissues and that the resultant modification of the chemical constitution of the body produces a therapeutic effect. (5) The temporary alleviation of pain often found after ionic medication is the result of a counter-irritant action. Campbell believes that there is little scientific foundation for the theory or practice of ionic medication.

**Rheumatoid Arthritis Treated with Intravenous Bacillus Coli Vaccine.**—PERKINS and WHITE (*Brit. Med. Jour.*, 1923, 1, 411) define rheumatoid arthritis as that type of chronic arthritis attacking the smaller and larger joints and characterized by proliferative changes in the ligaments and effusion into the joint cavities and going on to anky-

losis. This disease is considered an infectious one, though the foci of infection are usually very difficult to find; the commoner foci are the tonsils, alimentary tract and, especially in women, the genito-urinary tract. The treatment is divided into (1) elimination of focus of infection, (2) increase of resistance of the patient to the infection, (3) local treatment to the joint with the objects of (a) preventing deformity, (b) alleviating pain, (c) preserving movement of the joint. In the cases reported in the paper under discussion, careful examination failed to reveal any infected area; it was accordingly impossible to prepare an autogenous vaccine. The authors selected *B. coli* vaccine because it was readily obtained and easily administered. The normal defences of the patient suffering from rheumatoid arthritis are low and the object of the protein shock is to make a sudden call upon them with the idea of arousing them from their apathy. The vaccine was administered intravenously, the first dose varying from 50 to 200 million. A certain amount of difficulty was experienced in selecting a suitable initial dose; it should be large enough to produce a distinct reaction but not so large as to produce harmful effects. The reaction consists of a rise in temperature to 100 to 103° F., often accompanied by a chill, nausea and vomiting. The duration of the reaction varies from twelve hours to two days and during it the patient should remain in bed. If any improvement is to follow, it usually does so within two days but may not appear for three weeks. The shock treatment is advised in those cases in which no focus of infection can be found and in which the recognized methods of treatment have failed, and in early cases in which the processes in the joints are still active, especially if swelling and effusion are present.

**Observations on the Cause and Cure of Chronic Rheumatism.**—HARDING-FREELAND (*Brit. Med. Jour.*, 1923, 1, 281) defines rheumatism as an acute, subacute or chronic disease due to the invasion of the parts affected by a specific microbe, *Streptococcus rheumaticus* of Pointon and Paine. The treatment recommended is best summed up in the words of the author, "Experience . . . has led me to regard vaccine treatment as essential and other remedial measures as subsidiary, but by no means as unimportant, seeing that, in the vast majority of cases, they are usually desirable and often necessary." Of the 112 cases reported only 17 per cent failed to be improved by vaccine treatment; the cases "cured or markedly improved" number 93 and were distributed as follows: Articular rheumatism (arthritis) 52 cases, with 85 per cent "cured or markedly relieved"; muscular rheumatism (lumbago, etc.) 24 cases, 83 per cent greatly benefited or cured; neural rheumatism (sciatica, etc.) 20 cases, 75 per cent cured or markedly relieved; pharyngeal rheumatism (tonsillitis) 12 cases, all cured or markedly improved; cerebral rheumatism (chorea) 4 cases, all of which were cured and free from symptoms at the end of one year.

**The Scientific Basis for Non-specific Protein Therapy.**—In this paper CLARK (*Brit. Med. Jour.*, 1923, 1, 315) collects the available scientific evidence showing the nature of the effects produced by non-specific protein therapy. This method of treatment was developed along purely empiric lines and there soon appeared a strong prejudice in favor of the view that such treatment in order to be effective must be specific. It was early discovered that in many cases non-specific vac-

cines and sera were as specific as vaccines and that a large assortment of proteins and protein breakdown products produced the same effects as vaccines. Non-specific protein therapy has been recommended for the majority of known diseases but is of demonstrated value in relatively few. It yields good results in acute general infections such as typhoid fever, where after an exacerbation of the fever it frequently causes termination by crisis; the treatment is also successful in chronic infections, with local lesions in which the injection causes a febrile reaction followed by general improvement in well-being. The local lesions become acutely inflamed during the fever but subsequently heal quite rapidly. Non-specific protein therapy is also valuable in the treatment of acute and chronic arthritis, gonorrhea and anthrax. The injection of proteins, products of protein breakdown and the rapid destruction of body cells all produce a similar reaction; it is probable that they all have a common active principle, namely, a product of protein decomposition. Proteoses and albumoses are very toxic while peptones have a much less poisonous action. The effects of commercial peptone, protein poison and histamine are similar and resemble anaphylactic shock. It is difficult to understand why such a reaction should be of therapeutic benefit. There is no doubt that an excess of protein breakdown products is intensely toxic; traumatic shock appears to be due to protein breakdown products and the toxemia of intestinal obstruction is ascribed to the absorption of proteoses. In employing products in therapy it is essential that the doses be properly graded, for an overdose is extremely dangerous both in its immediate and ultimate effects. The reaction is of benefit only if it is of a certain intensity. The most important effects of protein therapy seems to be a change in the permeability of the capillaries; this is first increased and subsequently decreased. The former leads to an increased flow of lymph which washes into the blood stream a large variety of the products of cell metabolism. The blood changes following protein injection are immediate leukopenia followed by leukocytosis, an increase in the number of young and atypical red blood cells and an increase in the number of platelets; there is also an increase in fibrinogen, globulin, thrombo-kinase, blood sugar, non-protein blood nitrogen, proteoclastic ferments and antibodies. It appears, therefore, that non-specific protein therapy causes a washing out of the tissue fluids into the blood, resulting in important changes in the composition of the latter. Which of these changes is of primary clinical import remains to be determined.

## PEDIATRICS

UNDER THE CHARGE OF

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**Nasal Diphtheria.**—IAMS (*Atlantic Med. Jour.*, 1923, 26, 448) points out that primary infection of the nasal mucosa with the diphtheria



bacillus is not infrequent. It is often exceedingly mild and is not diagnosed because the possibility of its presence is not recognized. The symptoms as outlined in the average text-book, with the exception of the nasal discharge, either do not appear at all or are late symptoms, and are evident only after some days. The theory as to the extreme toxicity of this type was derived largely from the fact that only advanced and serious cases were diagnosed. The mortality is at least no higher than in the faucial type if sufficient antitoxin is given. All severe cases of rhinitis, particularly if unilateral, should be cultured. Many unexplained infections occur and can only be cleared up when the importance of nasal as well as faucial cultures is recognized. As so many cases are not diagnosed, epidemics are bound to occur, and the prevention of these can only be secured by cultures from the nose as well as from the throat.

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**Osteomyelitis of the Ilium in Children.**—BEARSE (*Jour. Am. Med. Assn.*, 1923, 80, 991) says that the cause of osteomyelitis in the ilium are the same as in osteomyelitis of other bones. The systemic manifestations are also the same, but the local symptoms are likely to be deceptive in that they are usually referred to the hip joints and not to the ilium. The diagnosis is made on the localized tenderness in the acute cases and on the swelling in the chronic cases, and there may be spasm of the muscles of that buttock and below it. There are pain and spasm in that hip on attempted motion, but with care motion can be obtained. The roentgen-ray is a decided aid in old cases, while in acute cases it may show nothing. Stereoscopic plates may help, but once the disease is localized the roentgen-ray is an aid in watching the progress of the disease. The course of the disease in the ilium is similar to that in the flat bones. It is evident that in infection of a flat bone with a thin cortex there will be early perforation, and if the disease progresses, there will be extension of this perforation or a new perforation will appear nearby. By roentgen-ray this is first evidenced by a punched-out appearance or rarefaction which may gradually increase in size. In advanced cases where there are several perforations the bone may take on the appearance of being mottled or moth-eaten. Complications are frequent. Some of these are dislocation of the head of the femur because of erosion of the acetabulum, metastatic infections of other bones, amyloid liver, arthritis of the hip, erosion of the femoral artery, phlebitis of the iliac vein and the development of pus pockets. The treatment is based on general surgical principles and varies with the conditions found. Briefly it is early operation with adequate drainage and removal of dead bone up to resection of the entire ilium.

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**Dietary Consideration in Infantile Eczema.**—GERSTLEY (*Jour. Am. Med. Assn.*, 1923, 80, 1141) has found that eczema develops in those who are overweight and underweight as well as in those with an adenopathy and also in those without, in those with flabby subcutaneous tissue and also in those with firm subcutaneous tissue. A characteristic common to most, namely, blue eyes, blonde hair and skin of very fine delicate

texture, can be attributed to a simple deficiency of pigment. He outlines a prophylactic treatment. He brings the skin of the predisposed fair-haired, blue-eyed children to the best possible state of nutrition. Irritants at times bring hyperemia and papule formation to sensitive cheeks, but the application of a mild protective salve of any sort, such as cold cream, is sufficient to prevent spreading of the process. If the diet is absolutely unchanged, these findings soon disappear. They may reappear again at intervals but rarely become very marked. If the skin of an infant is maintained in a state of good nutrition from the time of birth and at the same time protected from irritants, eczemas rarely appear. The active dietetic treatment from the standpoint of the pediatrician is that which brings the child most rapidly to the best possible state of nutrition. No one particular diet helps and no one particular diet does harm. The main consideration is to place the welfare of the entire body above the welfare of an individual organ. If this is carried out, local symptoms gradually disappear in proportion to improvement in the general condition. There are only two indications for restriction of the diet. The first is in an overfed baby with an oozing eczema, in which case reduction of food intake is of value. The other is in an infant in whom the eczema has become secondarily infected. A temporary reduction in diet by depleting the tissues of fluid, dries the cheeks and leaves a field less fertile for bacterial growth. In these instances there is no special indication for restricting any particular element of food. Restriction in quantity is all that is necessary.

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**A Statistical Study of the Tuberculin Test in Infancy and Early Childhood.**—WAHL and GERSTENBERGER (*Arch. Pediat.*, 1923, 40, 143) report a study of the tuberculin test performed upon exposed, suspicious or actively tuberculous individuals of those applying to the Babies' Hospital of Cleveland from 1907 to 1921. They found that a slight increase of the positive tests in the females over the males, the former giving a positive percentage of 61 per cent and the latter a positive percentage of 54. There was an increase in the percentage of positive reactions corresponding with the increase in age, being 35 per cent in infants under six months and 87 per cent in young children between thirty-six and forty-eight months of age. Of the different races and nationalities the colored race gave the highest percentage of positive reactions. Patients exposed to two or more sources of tuberculous infection showed a higher percentage of positive reactions than those exposed to only one. When only one source of contact existed for a patient, the mother was found responsible for the highest percentage of positive reactions, a brother or sister for the next highest and the father for the lowest of the group. Children giving a negative history of exposure showed only 15 per cent of positive reactions as against 44 per cent for those having a positive contact. In other words, 44 per cent of the children giving positive tuberculin tests gave a definite history of the tuberculous contact, while of those giving a negative history of exposure only 15 per cent reacted positively. Scrofula gave the highest percentage of positive reactions and was followed by pulmonary tuberculosis, tuberculous adenitis, tuberculous osteomyelitis,

tuberculous meningitis and pulmonary miliary tuberculosis. By using the intracutaneous test, controlled by checking with a known case of tuberculosis, a higher percentage of positive reactions can be obtained, especially in cases of tuberculous meningitis and pulmonary miliary tuberculosis than has been usually reported. The intracutaneous test, 0.1 cc of a 1 to 100 solution, is in practically 100 per cent of the cases more sensitive in its reaction than the tuberculin tests performed either by the tattoo or the burr method. In the same way the test performed by the tattoo method is more sensitive than by the burr method, although the first is more difficult from a technical standpoint. The intracutaneous test with a 1 to 1000 solution has always been found positive even when stronger dilutions of 1 to 10 or 1 to 100 were used. The reactions with the stronger solutions have been in general more marked, but the reaction with the 1 to 1000 dilution has been sufficient to convince the authors to choose it as their standard in performing the intracutaneous test.

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**Brain Tumors in Young Children.**—WOLLSTEIN and BARTLETT (*Am. Jour. Dis. Child.*, 1923, 25, 257) in 7 cases of tumor of the brain in children between the ages of two weeks and three years found that the average age was fifteen months. All of these tumors were gliomatous in type. Two were supratentorial and five were infratentorial. Of the supratentorial tumors, one occupied the left cerebral hemisphere and was congenital in origin. The other occupied the basal ganglia. In the 5 infratentorial tumors the vermis of the cerebellum was involved. The growth involved the right cerebellar hemisphere in four and the left hemisphere in only one instance. The medulla and the pons were infiltrated in 2 cases and the right cerebellopontile peduncle was involved in 2 instances. The upper cervical cord was compressed in 3 of the cases. Hydrocephalus was present in all of the 7 cases. The most striking feature of the symptomatology was the variability in the physical signs. Convulsions were absent in all cases except one in which a convulsion occurred just before death. Vomiting did not appear as a significant symptom in any of the cases. The spinal fluids showed nothing that was distinctive. Xanthochromia was present in only 1 case in which there was a cerebral hernia.

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**The Characteristics of the Cerebrospinal Fluid in Postdiphtheritic Paralysis.**—REGAN, REGAN and WILSON (*Am. Jour. Dis. Child.*, 1923, 25, 284) carried out a study of the rachidian liquid to determine whether a meningeal reaction occurred in the spinal fluid in postdiphtheritic paralysis and to assist in establishing the cytological and chemical formula in that disease. A series of 28 specimens of spinal fluid from 16 patients were examined at various intervals from the second day to the eleventh week of the paralysis, 22 being in the first four weeks. Nearly two-thirds of the patients had extensive generalized paralysis and in 5 death occurred. These paralysees followed usually a moderately or very severe initial angina, commonly of a polymicrobial or septic form, with extensive membrane formation and frequently accompanied by myocarditis. They draw conclusions from the findings in this

series combined with those of a former series. They found that the cerebrospinal fluid in postdiphtheritic paralysis is a clear limpid fluid flowing usually under normal or slight hypertension. The Bordet-Wassermann reaction of the spinal fluid was uniformly negative in each case. The cell count was always within the normal limits, less than 10 cells per c.mm., and the cells found were small lymphocytes. The globulin was increased in a minor proportion of the patients, less than one-third. The increase was slight, occasionally moderate and never marked. There existed in certain cases less than one-third, a dissociation between the cytological and chemical findings. The colloidal gold reaction was the most constantly positive pathological reaction encountered in the fluid in this disease. The reduction usually occurred in the syphilitic zone, occasionally extending into the higher dilutions. The reaction seemed gradually to subside, reaching normal as convalescence was established and paralysis disappeared.

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**Transfusion through the Umbilical Vein in Hemorrhage of the Newborn: Report of a Case.**—SIDBURY (*Am. Jour. Dis. Child.*, 1923, 25, 290) remarks that the obtaining of blood from one of the superficial veins of the newborn infant is often a difficult task and is at times even impossible in the hands of an expert. The easiest route is by way of the superior longitudinal sinus, but this route should only be employed by one familiar with its use; but even the experienced worker may fail to enter the sinus because of its distortion from its usual location as a result of molding of the head. This is especially true during the first few days of life. So far as the author knows this method has never been used before, but it appealed to him as a rational method, for the baby had been receiving blood and nourishment through the umbilical vein up until three days previously. The umbilical vein was patent and accessible for transfusion up to and including the fourth day of life. It is up to the fourth day of life the most accessible vein, in a newborn baby, if patent. The probability of a clot in the umbilical vein is very unlikely because the blood is fluid many hours after death in these cases. Transfusion through the sinus in cases of intracranial hemorrhage may increase intracranial pressure, which is not desirable. Transfusion through the superior longitudinal sinus is comparatively simple for one experienced, while the umbilical route is simple enough for those inexperienced in the sinus route. In the case reported 100 cc of blood was introduced through the umbilical vein. In doing this the cord was cut just proximal to where it had been originally ligated. A regular transfusion needle was introduced into the lumen of the largest of the three vessels that were present. This was the umbilical vein. A ligature held the needle in place. First 20 cc of physiological salt solution was injected slowly. The mother was the donor, and five injections of 20 cc syringefuls of the untreated blood of the mother were injected, after which 10 cc of physiological salt solution was added to clear the needle and the vein of blood. After the withdrawal of the needle the stump was tied off as before. There was marked improvement after the injection, and there was a slight febrile reaction following it.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Sodium Thiosulphate.**—McBRIDE and DENNIE (*Arch. f. Dermat. u. Syph.*, 1923, 7, 63) report upon the use of sodium thiosulphate in the treatment of arsenical and other heavy metal poisonings, with special reference to the use of this drug in arsphenamine dermatitis. The chemically pure preparation may be given intravenously in doses up to 2 gm. without toxic effect. The action depends upon the sulphur content of the drug and is in keeping with the familiar practice of using sulphur derivatives, such as calcium sulphite in the treatment of heavy metal poisoning. Immediately upon the appearance of the arsphenamine dermatitis, doses of 0.3, 0.45, 0.6, 0.9, 1.2 and 1.8 gm. were given on as many successive days. It is possible to give a larger dose at the outset without ill effect. A number of case reports, showing the results of this mode of treatment, are given.

**The Course of Syphilitic Infection in Pregnant Women.**—MOORE (*Johns Hopkins Hosp. Bull.*, 1923, 34, 89) discusses the results of the survey of 178 pregnant women with positive blood Wassermann reaction and 22 non-pregnant mothers of syphilitic children. Of his series, 22 per cent had outspoken lesions of early or late syphilis at the time of admission. Of the remainder, in only 21.5 per cent were all evidences of syphilis except the positive blood Wassermann reaction lacking. The author feels that he has confirmed and amplified Hutchinson's clinical observations in 1876, which led him to the conclusion that all mothers of syphilitic children are themselves syphilitic and that suppression of syphilis by pregnancy and distortion of the usual time relations of the disease by pregnancy, is an established fact. If impregnation and infection approximately coincide, or if the infection occurs during the course of pregnancy, early but apparently mild manifestations of syphilis may develop. Approximately one-half of the patients thus infected exhibited a reduction in severity of the manifestations of the disease. A slightly larger proportion, infected with syphilis at about the time of impregnation, failed to develop any of the usual early lesions of syphilis. In occasional cases, the usual time relations between primary and secondary syphilis are much prolonged; on the other hand, the interval between early syphilis and tertiary syphilis may be much shortened, and grave lesions of a tertiary type may occur early in the course of the disease. The protection against the early lesions of syphilis afforded by pregnancy may persist over a long period of years and possibly a lifetime. Spontaneous cure of syphilis seems in a few instances to have been the ultimate result. Those women of the author's series who developed late syphilis were especially prone to syphilis of the viscera and of

the cardiovascular apparatus, whereas tertiary lesions of the skin and bones and neurosyphilis, either clinical or symptomatic, were rare. In 33 of the 200 patients, the blood Wassermann reaction gave fluctuating and anomalous results. In 10 per cent of the pregnant women with secondary syphilis, the reaction was negative. A negative or a positive reaction during pregnancy may be spontaneously reversed after the birth of the child. In 2 instances, it was suggested that this variability in the Wassermann may be due to an excess of native amboceptor in the blood in certain women during pregnancy. It was observed that the ice-box Wassermann may be strongly positive when the water-bath test is negative. In another survey, the author found that the incidence of abnormal spinal fluids in women with late syphilis was twice as high in a group of sterile women as in a similar group in which one or more pregnancies had occurred since infection. The mechanism of suppression in the pregnant woman is still undetermined.

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**Prophylactic Treatment of Syphilis.**—NICHOLS and WALKER (*Jour. Exper. Med.*, 1923, 37, 525) report the results of experimental observations on prophylactic treatment in syphilis. The authors' work is of special interest because of their discussion of the significance of the natural spirochetosis of rabbits (infection with *Spirochetæ cuniculi*) on the experimental study of syphilis in rabbits (infection with *Spirochetæ pallida*). The authors conclude that rabbit spirochetosis does not give rise to a positive Wassermann reaction, while human syphilis in rabbits sometimes gives rise to a positive Wassermann reaction. The course of the lesions on the scrotum and genitalia in natural spirochetosis differs from that in syphilis, and the authors believe a morphological differentiation is possible. The principal purpose of the work was to demonstrate the complete curability of syphilis in an experimental animal by the use of arsphenamine and the authors assert that complete cure is unquestionably possible with one or several doses of arsphenamine. They do not insist that this constitutes a demonstration of curability in man, but they believe that it indicates that cure is possible with sufficient treatment. In testing the value of calomel prophylaxis, they found that it was effective up to eight hours after inoculation and that the ointment base is a matter of less importance than has been supposed. Gland transfers from animals with positive local inoculation yielded 87.5 per cent of takes. Gland transfers in rabbit spirochetosis were negative. The authors feel that rabbit spirochetosis need cause no more serious errors in the study of experimental syphilis than have been produced by the identification of other acid-fast bacilli in the study of tuberculosis in man. They feel that the effects of rabbit spirochetosis are comparable to those of Vincent's angina in man. In studies of generalized syphilis supposed to involve the genitalia and in sexual transmission experiments, *Spirochetæ cuniculi* may be a serious complicating factor.

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**The Treatment of General Paresis by Induced Infection with Malaria Plasmodia.**—PILCZ (*Lancet*, 1923, 204, 19) directs attention to and summarizes the results of the treatment of general paresis by induced infection with tertian malaria according to the technic of von Wagner and Gerstmann. The technic, as described, consists in the injection

of 2 cc of blood from a patient with tertian malaria (not tropical malaria), beneath the skin of the paretic patient's back. This blood must be obtained by venipuncture during the attack of fever. After one or two weeks, on an average, the paretic develops his first malarial attack. After some ten or twelve attacks, the malaria is checked by quinine during the first three or four days (0.5 gm. of quinine sulphate twice a day for three or four days and then once daily for two weeks). At the same time, a course of neo-arsphenamine, 0.3 gm. to 0.6 gm., is begun. Acoustic hallucinations and accentuations of other symptoms are occasionally observed during the malarial stage, but disappear promptly when the quinine cure is started. Of 141 paretic patients treated in 1919-1920, 51 have completely recovered, 18 showed marked and persisting remission without being able, however, to return to their former occupations, 57 cases became stationary or showed incomplete remission, and 15 patients died. Simple dementia and the maniacal types show the most favorable prognosis. The development of remission is gradual, and not necessarily parallel in degree or duration with serological reaction. Some good results are claimed in tabes and disseminated sclerosis. Pilez further emphasizes the fact that in a survey of 5000 soldiers in whom a 5 per cent incidence of paresis was observed, only 1 of the affected patients had ever had a febrile disease, and those who had undergone febrile infections in no case developed paresis. The author suggests that tropical climates and early treatment by induced fever may have some influence on the course of neurosyphilis.

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**Lacquer Dermatitis.**—PUSEY (*Arch. Dermat. and Syph.*, 1923, 7, 91) reports a case of lacquer dermatitis which occurred in a patient whose business consisted in the selling of cheap lacquered Japanese canes carrying small flags. The lacquer employed on these canes is made from the Japanese lacquer tree (*Rhus vernicifera*), and the dermatitis it produces has been known in Japan and China for more than a thousand years. Toyama's work indicates that the lacquer from jars buried a thousand years has the same irritant properties as the fresh preparation. The condition is rarely recognized in this country. It yields readily to wet dressings of dilute aluminum acetate solution.

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**The Resistance of Hair to Certain Supposed Growth Stimulants.**—MILDRED TROTTER (*Arch. Dermat. and Syph.*, 1923, 7, 93) reports a series of investigations of the effect of petrolatum, of sunburn and of shaving upon the growth of hair. The method employed consisted of the measurement of hairs in different regions, hairs being removed by tweezers at various intervals after a single close shave. It was found that the rate of growth of hair was in a measure proportional to its area of cross-section, which was greatest in the axilla and scalp and least upon the arm. The average life of the hair upon the arm or leg is approximately eleven weeks. The popular supposition as to the effect of petrolatum, of sunburn and of shaving in stimulating the growth of hair could not be substantiated, no apparent change in rate of growth resulting from them. All three of these supposed stimulants were given a thorough trial so the results appear reasonably conclusive. No change in the type of hair growth appeared to result from any of the procedures employed.

## OBSTETRICS

UNDER THE CHARGE OF

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**Cesarean Section for Double Uterus.**—SHOEMAKER (*Jour. Am. Med. Assn.*, 1923, 80, 103) reports the case of a primipara who upon examination was found to be several months pregnant and to have a double uterus, cervix and vagina, with the pregnancy in the left side of the uterus. She had a spontaneous abortion, in the early months. From this she made a good recovery, and afterward menstruated regularly from both uteri. Later she became pregnant in the right uterus, which gradually enlarged; the left remaining as before. The patient's pelvis was flat. During the remaining months she did well and was threatened with an abortion, but hemorrhage stopped with rest in bed. The vaginal septum was so fibrous as to be an obstacle in labor, and it was impossible to tell the thickness of the wall which divided the two uteri. It was feared that the uterus would rupture during labor. An elective section was decided upon, but the patient came into labor several weeks before the time and was brought to hospital. On examination the right uterus completely filled the right flank and right hypochondrium. The left uterus was about the size of an orange. The child was quickly delivered from the pregnant uterus and each half was found to be apparently a separate organ. The tubes were doubled, ligated and cut, and the uterus was closed. The recovery of mother and child was uncomplicated.

**Use of Pituitrin in the Third Stage of Labor.**—SEIDES (*Surg., Gyn. and Obst.*, January, 1923, p. 108) treated 500 consecutive cases of parturition by giving each 0.55 cc of pituitrin at the beginning of the third stage of labor. Nothing was done to the uterus except to palpate it sufficiently to find whether the placenta had left the uterus. The patient was made to expel it from the vagina by voluntary effort and the medical attendant made some pressure and gave some support to the recti muscles. Among these cases was one of simple retention of the placenta, and three cases where the placenta failed to separate and required manual removal. The contraction of the uterus was well maintained. The loss of blood was very small and involution went on more rapidly than usually. After-pains were less frequent and less severe. The general health of the patients was considerably enhanced. This experience would indicate that such use of pituitrin considerably shortens the third stage of labor, prevents bleeding, lessens blood loss, lessens and shortens the lochial discharge, and has a tendency to do away with manual compression of the uterus and manual expression of the placenta. Involution is better; after-pains are lessened, and the placenta is not so often retained. The writer believes that pituitrin will not cause retention of the placenta, because



it simply increases the normal uterine contractions which are intermittent and does not produce a tetanic condition of the uterine muscle. He believes that many cases of retention of the placenta arise from excessive or improper manipulation of the uterus, and if this can be done away with the placenta will not be retained.

**The Anesthetization of Patients for the Classical Cesarean Section.**—SPENCER (*Brit. Med. Jour.*, 1922, 2, 905) described his usage in anesthetizing patients for cesarean section. He wishes to avoid the dangers to the fetus which result in the deep anesthetizing of the mother and he also wishes to spare the mother so much as possible. Whenever an operation is required he insists that a competent anesthetizer, especially trained, should administer the anesthetic. He believes that the disadvantage of ether is the fact that it leads to asphyxia in the infant when given to a surgical degree. Chloroform exerts its influence in such small quantity that surgical anesthesia is not reached, and hence its effect upon the fetus is very little. From his experience, Spencer has been led to omit hypodermic injections before cesarean section and to give the anesthetic to the patient while upon the operating table, and not in an adjoining room. Chloroform is then given and the child is rapidly delivered, usually in thirty or forty seconds from the commencing of the incision, and in his experience always breathes and cries at once. For the remainder of the operation ether is given, usually by the open method. If there is an unusual loss of blood, pituitrin is administered by hypodermic injection. Where the classic cesarean section is done before or soon after the onset of labor, the child is born free from asphyxia and cries at once.

**Is Interference Justifiable in Prolonged Labor?**—BECK'S (*Am. Jour. Obst. and Gynec.*, 1922, 4, 623) paper is based upon what he terms a "sense of security" obtained by the use of his two flap low incision cesarean section. If after prolonged labor a patient cannot deliver herself she can safely be delivered, the writer thinks, by this method. During a prolonged labor the patient is given as much rest as possible. Nourishment is administered freely. An abdominal binder is tightly applied so soon as the membranes rupture if the cervix is almost dilated. The patient is urged to make voluntary effort. Liberal doses of morphine are often given, and whenever the character of the contractions shows that the uterus is fatigued, sufficient morphine is given to stop the labor and allow the patient to sleep. In 1138 hospital confinements there were 79 long labors of whom 66 were delivered spontaneously. There were six forceps cases because of marked change in the fetal heart-rate or prolonged second stage. There were two breech extractions and five cesarean sections. These later were done in cases of relative disproportion where engagement failed after a thorough test of labor. The infant mortality was 7.6 per cent. One mother died on the third day after cesarean section. Of the entire series of 1138 deliveries the total infant mortality was 3 per cent, maternal mortality 1 in 569 cases. These results the writer considers satisfactory in comparison with those obtained by interference. For reasons which he does not state he believes that this method calls for considerable courage on the part of the attending obstetrician, and is

accompanied by considerable worry. If the writer has a "sense of security" which he has obtained by the use of his two flap low incision cesarean section, why worry? [REVIEWER].

**Is the Usual Method of Preparing Patients for Delivery Beneficial or Necessary?**—JOHNSTON and SIDALL (*Am. Jour. Obst. and Gynec.*, 1922, 4, 645) have studied various types of labor, and compared results, not only of methods of preparation, but also of delivery. The writers believe that many factors play a part in the causation of morbidity in parturition, operative interference doubling the percentage. Regardless of sterile gloves vaginal examination increases the danger to the patient. Catharsis and lacerations of the perineum do not influence the puerperal period. When the membranes rupture prematurely, it is not the length of time the uterus is drained, but other factors which cause morbidity. With a limited number of patients who had no routine preparation, better results were obtained than among those who had. It is suggested that picric acid as an antiseptic is better than iodine and other antiseptics in use. The strength employed is not mentioned.

**Rigidity and Stenosis of the Cervix Complicating Labor.**—FÜTH (*Zentralbl. f. Gynäk.*, 1922, 46, 1671) in his practice, observed a boy aged two, who had upon the head an area 2 or 3 cm. wide, white in color and without hair, and resembling a scar, which was two fingers' breadth above the ear. This scar could be pushed over the cranial bone and was adherent in one point near the forehead. Immediately after the birth of the child there had been a very considerable tumor upon the head, which resulted in gangrene of the skin, and from this gangrene had resulted the scar in question. The cause of this scar and gangrene had been birth pressure from the extraordinary rigidity and tightness of the cervix at the time of the child's birth

## GYNECOLOGY

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**Treatment of Uterine Cancer.**—Whenever the subject of the treatment of uterine cancer is under discussion, it is noticeable that there is a distinct plane of cleavage between the classical gynecologists and the radiologists, the former preferring operation at any hazard, the latter blinded by the wonderful results which have been accomplished

by radium under proper conditions. The rank outsider, in his search for the latest information, does not know which camp to follow. Under such circumstances, it is a professional blessing that there are a few men who are as well trained on the one side as on the other and whose opinions, therefore, are unbiassed, but based upon actual clinical experience with both methods of treatment. One of the foremost men of this type is SCHMITZ (*Northwest Med.*, 1923, 22, 77), who divides uterine carcinoma into five groups: Group 1: The *localized* carcinoma; the neoplasm is clearly confined to the uterus after a physical examination. Group 2: The *borderline* carcinoma; it is doubtful after a physical examination whether the neoplasm is still confined to the uterus or has begun to invade the neighboring tissues, organs or regional lymph nodes. Group 3: The clearly *inoperable* carcinoma, in which an invasion of the neighboring tissues and organs or regional lymph nodes can be demonstrated. Group 4: The *advanced* carcinoma characterized by a "frozen pelvis," a marked cachexia or distant metastases. Group 5: The *complicated* carcinoma; the cancer may be limited to the uterus, but grave constitutional diseases exist. A localized cervical carcinoma can be safely eradicated by an abdominal or vaginal panhysterectomy. The abdominal operation is preferable and after opening the abdominal cavity we should proceed at once to the regional lymph nodes and adnexa. If they are found to be infiltrated, it is useless to proceed with the panhysterectomy, but the operation should be simply exploratory. If an abdominal operation is difficult of execution on account of extreme obesity or mild forms of heart and kidney disease, then the vaginal procedure must be chosen, although it is not possible to explore the pelvic organs as satisfactorily as through an abdominal incision. The Wertheim extended radical abdominal panhysterectomy has a high primary operative mortality, varying from 15 to 25 per cent. It is difficult of execution, accidents are frequent, such as vesical fistulæ and injuries to the ureters and rectum. The advantages claimed for it as to permanent cures are lost by the high primary mortality and, therefore, it can never find a place in our clinics. The accidents during the operation, the primary mortality and the percentage of recurrences increase rapidly if we subject borderline cases to surgical eradication. The possibilities of totally eradicating all carcinoma elements are improbable and infinitesimal. Operative procedures applied to such cancers have tended to discredit surgery, consequently the laity and the general practitioner have realized this state of affairs and hesitate to recommend or to resort to surgical treatment, even if the disease could be successfully eradicated thereby. Confidence of the medical profession and the laity in the surgical treatment can only be reestablished by an honest adherence to the one indication for surgical treatment of cancer of the cervix—it must be clearly localized within the uterus. Carcinomata of Groups 2 to 5, therefore, contraindicate surgical removal. Unfortunately, the number of malignant neoplasms of these groups form the larger percentage of cancers entering our clinics, the percentage being as high as 80 to 90. The success of radiation therapy depends upon the solution of the problem that a dose of rays must be applied to the deeply seated cervical cancer which will kill it without permanently traumatizing the neighboring healthy tissues and organs, as the bladder, the rec-

tum and bowels. This can be accomplished by the newer technic of radiation therapy for deeply seated malignancies. Of 109 cervical cancers which the author treated between 1914 and 1917, 12 are alive and well. If we subtract the recurrent cases that were operated upon and later on came for treatment of recurrence, namely 31, and the advanced cases, numbering 19, which are treated only palliatively, as they cannot be treated by any known methods of treatment; then there are 59 cases of cervical carcinomata of Groups 1, 2 and 3 with 11 cures, that is, 18.75 per cent. However, if we consider only those cases that possibly would come under the category of surgical statistics, *i. e.*, Groups 1 and 2, we have 14 cases with 6 five-year cures, or 42.85 per cent. Subjecting the statistical results to a minute study, we are at once surprised at the poor results obtained in the last two groups, namely, the advanced and the recurrent cases. Indeed, it is a fact that radiations will cause only a temporary alleviation of the symptoms of the cases in these groups. At times we may observe a case that appears to be subjectively and anatomically relieved, but this relief lasts only for a short while. We also must be careful in the application of the rays in the cases belonging to this group, as otherwise the toxemia caused by the rays may be so severe as to kill the patient. The natural power of resistance to the toxemia is so weakened that the patient can no longer activate sufficient defensive force to tide her safely over the period of reaction. Hence, in this class of cases we attempt to relieve the symptoms by a small dose of radium of about 600 to 1000 mc. hours. Should the regional lymph nodes be involved, and the vaginal fornices and surrounding tissues be free of any recurrence, then the application of a full dose of roentgen-rays is indicated. We often read the statement that, whenever possible, radiation treatment should be combined with surgical procedures, instituted either preceding or following the application of the rays. The author is of the opinion that such procedures do not benefit the patient; on the contrary, she invariably becomes refractory to the rays or has an early recurrence. He also warns against a repetition of the radiation treatment, since, if it has been correctly applied as regards dose and technic, a second application cannot improve the results of the first treatment. The effects of the radiation upon the tissue wear off very slowly, so that from nine to eighteen months pass by before the normal and diseased tissues have completely recovered from the injuries of the first radiation. In answer to the question of whether surgical treatment of a localized cervical carcinoma should be preceded or followed by radiation, the author states that this is unnecessary if the case was truly early and localized. Should the surgeon be in doubt as to the total eradication of the cancer cell elements, then a course of ray treatments should follow, which must be as intense as if the operation had not been performed. The uterine body is replaced by a phantom uterus made of Bakelite, which is inserted between the folds of the broad ligament by removing the row of sutures closing the vaginal roof. Without the use of the phantoms, we cannot apply a dose of gamma rays which would suffice to enhance the action of the roentgen-rays.

## HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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**Rocky Mountain Spotted Fever: Infectivity of Fasting and Recently Fed Ticks.**—SPENCER and PARKER (*Pub. Health Rep.*, 1923, 38, 333) show the fallacy of depending upon tick-feeding experiments to determine the infectivity of ticks and suggest a combination of feeding and inoculation. Feeding on a healthy animal apparently has the quality of reactivating the dormant virus in an infected tick. It is suggested that the work may explain why so few human infections occur, that is, the ticks may be removed before reactivation. It may also indicate that in time the virus may die out in the ticks.

**A Toxin-producing Anaërobe Isolated Principally from Fly Larvæ.**—BENGTSON (*Pub. Health Rep.*, 1923, 38, 340) shows that the botulinus group is made up of at least three types based upon immunity tests, though but two are known to be pathogenic for man; the third probably is toxic for fowls. The cultural and immunological relations do not necessarily run parallel.

**The Effect of Vaccinia upon Leprosy.**—HASSELTINE (*Pub. Health Rep.*, 1923, 38, 1) found that in a considerable percentage of cases, lepers reacted to vaccinia by developing a rash in the form of red, infiltrated areas, which declined with the decline of the vaccinia. Desquamation of epidermis followed in some cases. Constitutional symptoms were observed, such as chilliness, fever, malaise. Nodular leprosy and the mixed varieties show the peculiar manifestations, anesthetic cases being little affected.

**Eight Years of Epidemic Poliomyelitis in Montana.**—SIPPY (*Public Health Rep.*, 1923, 38, 135) presents the following conclusions based upon eight years' experience: (1) The study of poliomyelitis in Montana indicates that the disease does not originate without previous contact with infected individuals. These infected persons may be only: (a) Immune carriers; (b) sufferers of mild or abortive attacks; or (c) recognized cases. (2) With the exception of a few cases in isolated rural areas, outbreaks tend to occur along principal interstate and intrastate travel routes. (3) Considerable distances between Montana cities afford some natural protection against rapid spread of the disease. (4) Without large, congested population centers, little opportunity is

afforded for acquisition of immunity by contact with mild infections. Rapid spread and a fatality rate higher than usual may ordinarily be expected in isolated communities when infection is introduced. (5) Isolation or quarantine control measures are clearly ineffective without a common knowledge of the importance of recognition of the mild and abortive type cases. (6) The value of antipoliomyelitic serum is regarded as neither proved nor unproved. Its use appears to be without harmful results, of possible advantage and apparently worthy of further administration and study.

**The Trachoma Problem in the State of Minnesota.**—CLARK (*Pub. Health Rep.*, 1923, 38, 383) reports that in 1912-1913, 1 case of trachoma was found to 640 white population and 1 among each 7 of Indian population. The incidence in Indian day schools was 10.48 per cent and in boarding schools 23.86 per cent. In 18 per cent of the cases there was marked injury to vision. In public schools and state institutions the incidence was very low. A more recent survey, December, 1922: Though the figures are not so large, it is believed that the latter survey shows an increased menace in many places and some new foci. In general, it is believed that the disease is fairly well circumscribed. The following recommendations are made: (1) An educational campaign should be inaugurated properly to inform the citizens of the state of the injurious effect of trachoma on vision, its curability and the methods of prevention and control. (2) The regulations of the State Board of Health mandatorily requiring notification of trachoma should be more strictly enforced, and a strong attempt should be made to enlist the coöperation of the physicians of infected districts in detecting existing cases and in eliminating foci of infection. (3) A detailed trachoma survey of the entire Indian population of the state should be made, including isolated Indian bands, for the purpose of locating every infected Indian within the state, with the view of securing proper care of and attention to individual cases and of preventing the further spread of the disease. (4) A careful examination should be made of every child enrolled in the public schools contiguous to the Indian reservation and in those at the different mining locations in the state, and the name and address of every infected child should be recorded and certified to the State Board of Health for such action as may be necessary for the ultimate elimination of this disease from the school population and the homes of these districts. (5) A complete examination of the eyes of every inmate confined in or attending a state institution should be made to detect cases of trachoma for the purpose of ensuring prompt and adequate treatment. (6) A mobile trachoma unit should be organized at state expense and authorized to travel to infected points for the purpose of giving necessary treatment and familiarizing the local physicians with the most recent and effective methods of cure. (7) Arrangements should be perfected whereby certain hospitals located at strategic points from the standpoint of trachoma prevalence, may be utilized, at state expense when necessary, for the hospitalization of infected cases requiring hospital treatment occurring in the white population. (8) In order more effectively to eliminate trachoma in the district formerly comprising the White Earth Indian Reservation, a hospital should be operated by the state

at some readily accessible point in this district for the proper management of all trachoma cases found among the former wards of the Government. (9) A coöperative arrangement should be entered into with the United States Office of Indian Affairs for the purpose of enforcing measures necessary for the control of trachoma among that portion of the Indian population of the state remaining under Government guardianship; otherwise, owing to improved facilities for intercommunication, the elimination from the non-reservation population will be greatly complicated, if not impossible.

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**A Preliminary Report on the Use of Creosote Oil as a Mosquito Repellent.**—COOGLE (*Pub. Health Rep.*, 1923, 38, 443) gives the following as a summary of his observations: "These observations indicate that creosote oil, when applied to the walls and ceilings of certain houses, in the quantity of 1 gallon to 420 square feet, will noticeably repel anopheline mosquitoes. The duration of its effectiveness is yet to be determined. Observations made of certain of the creosoted houses ten weeks after the creosote had been applied seem to indicate that the creosote oil was still effective. It appears the creosote oil as a mosquito repellent is particularly applicable to and desirable for use in houses of poor construction, where screening and other antimosquito measures cannot be effectively employed. Apparently colored people who commonly live in houses of this type in the southern states do not object to the application of creosote oil in the quantities employed in these observations. Unquestionably it is less objectionable than the smudges of rags, leather and feathers, so universally used by these people to keep the mosquitoes away while they secure a few hours' sleep. Apparently, the employment of creosote oil in the quantity and manner indicated above is perfectly safe. No ill-effects were noted upon any of those who slept in the rooms subsequent to the application of creosote oil. One observation seems to indicate that creosote may be used to prevent mosquitoes from laying eggs in water barrels."

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**Dried Milk Powder in Infant Feeding.**—CLARK and COLLINS (*Pub. Health Rep.*, 1922, 37, 2415) found the milk prepared from dried milk powder was quite satisfactory for infant feeding. Neither scurvy nor rickets seemed to follow the use of the preparation and the general results from the point of view of nutrition were good. This work confirms the impression gained earlier on less adequate data.

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ORIGINAL ARTICLES.

THE PROGNOSIS OF SYPHILIS.

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NEW YORK.

BECAUSE of the extensive and intensive educational propaganda regarding the prevalence and seriousness of venereal diseases a large percentage of the educated lay public has a superficial knowledge of their nature and results. This information is sometimes misleading and conveys impressions which tend rather to exaggerate than to properly measure their importance. After a patient with a syphilitic infection recovers from the first mental shock of the physician's diagnosis his next reaction is to ascertain the possibility of cure, the duration of treatment and the chances of developing certain sequelæ which he fears may follow. Will he ever be fit for matrimony and capable of begetting healthy children? How long is the disease contagious? These among other questions, confront all physicians who have to do with this class of cases.

Is the medical adviser who assumes the responsibility of treating and predicting the outcome of a case of syphilis sufficiently familiar with the course of the disease and with the effects of the specific remedies to be able to give an intelligent answer to these questions? Can he assure the anxious patient that a cure will follow treatment over a given period of time and that the most feared late results of the disease will not occur?

It is unfortunate that the majority of practitioners see only that phase of the disease which occurs in their particular work. Few have the opportunity to follow that patient from the initial infection through the varied possible clinical manifestations. Their



prognostic views are influenced by the phase of the disease they observe and the manner in which it responds to treatment. The visible accidents are treated until they disappear but the infection as a whole is seldom treated or followed by any sustained effort. It is only by piecing together scattered observations by clinicians, pathologists and serologists that we can obtain an imperfect conception of the prevalence and possibilities of this great infection.

An examination of the vital statistics when properly compiled supplies accurate information as to the cause of death in all diseases excepting the venereal group. It is comparatively easy to determine the average mortality from typhoid fever and to predict with a fair degree of assurance the outcome of a given case. Syphilis seldom or never appears in mortality statistics as the direct or indirect cause of death. It is not written on death certificates. The relation of cause and effect is lost sight of because of the long duration of the infection and the slowly progressive nature of the tissue degenerations which arise from it. Definite names which carry more respectability, such as myocarditis, aneurysm, cerebral hemorrhage, the renal complications of tabes are given as the direct cause of death, and the relatives and friends are comforted and deceived.

We have, therefore, at the present time no correct estimate of the incidence of syphilis owing to the large number of unsuspected and undiagnosed cases as well as wilfully concealed diagnoses. The statistics available give only the approximate prevalence as based on positive Wassermann reactions obtained in the army and navy, in general hospitals, institutions for the insane and in certain industries where the test is required, as among those who handle food. In hospitals positive Wassermann reactions have been obtained in 20 to 30 per cent of admissions; in insane asylums in 20 per cent. The percentage for our entire population is variously given as 5 to 20. Insurance statistics show that the mortality of the syphilitic is 33.3 per cent above expectations. Autopsy records, too, reveal a wide discrepancy according to the pathological criteria employed in the studies. Deaths from syphilis occur in individuals forty to sixty years of age as the result of myocardial, vascular, renal and hepatic disease not clinically recognized as syphilis. In 4880 autopsy records at Bellevue Hospital, Symmers found syphilis in 314 cases or 6.5 per cent. In a similar study by Warthin at Ann Arbor, during a ten-year period, the infection was found present in 300 cases or 40 per cent of the number investigated. Symmers' diagnosis was based on gross syphilitic changes such as aortitis, aneurysm, chronic interstitial orchitis and disease of the central nervous system, liver, bones, respiratory tract, and so on. Warthin's criteria were small focal lesions found in the various organs in addition to easily recognized gross changes.

It would be unscientific and illogical to prognosticate the future

of a syphilitic patient seen at an early stage of the infection and treated by modern specific drugs from the viewpoint of the pathologist or from the possible end-results of undiagnosed and inadequately treated cases. Fortunately, all syphilitics do not die of the infection. Cases aborted or cured by early treatment do not often favor us by dying of some intercurrent malady. We are, therefore, denied the absolute proof of cure insisted on by the pathologist and are obliged to rely on the revelations of the Wassermann reaction properly interpreted and controlled by the clinician, the occurrence of second infections, and the prolonged absence of clinical symptoms.

It would be a superhuman task to convince certain pathologists who claim that all syphilitics who come to autopsy with or without a positive Wassermann reaction are ever cured. On the other hand, it would be a task fully as difficult to convince an experienced clinician that syphilis treated at the opportune time and in the proper manner cannot be cured. Fortunately, the victim of the disease is not advised by the pathologist and is spared a lifetime of misery and fear by the sane knowledge of the clinician. He is cured, marries and has healthy progeny if fortunate enough to fall in the hands of a practitioner equipped with modern tools and the knowledge of how they should be used.

In the pre-Wassermann days the disease was said to be cured by so many years of treatment by the favorite pill or mixture of the doctor and the absence of visible signs of the disease. Syphilis was considered by many as less serious than gonorrhea. Jonathan Hutchinson repeatedly states in his numerous contributions to the clinical side of syphilis that the vast majority of those who have passed through an attack get well with or without treatment and remain well during the rest of their lives. The optimism of Hutchinson while concurred in by some of his colleagues was as vigorously denied by others who were more inclined to state that "once syphilis always syphilis." These opinions were largely due to impressions based on a more or less large clinical experience without a clear conception of the possibilities of the infection.

The prognosis of syphilis based on a larger grasp of the problem and the modern criteria of cure is on an entirely different basis than in the pre-Wassermann era. Then the absence of clinical symptoms, especially the external manifestations, was taken to indicate a cure of the infection. Immunity to new infection was considered in the same light as immunity to the acute exanthemata. The occurrence of second infections was rare and even disputed. Now numerous cases are reported in literature and are seen in every large clinic devoted to syphilis.

The physician who assumes the responsibility of treating and predicting the outcome of a case of recent syphilis or a case of syphilis in any stage, is handicapped by a lack of knowledge as to

all its possibilities. If he does not grasp the relation of early involvement of the central nervous system to its late degenerations how can he predict to an individual that he will or will not at some future time die from cerebral hemorrhage or become the victim of paresis or tabes? To the internist come the cases of aortic disease, myocarditis and aneurysm due to slowly progressive changes over years. The syphilographer should have enough knowledge of internal medicine to be able to visualize the future of his patient along these lines. He should in a word know all the tissue reactions evoked by the invasion of the treponemata and to what degree they can be influenced by our therapeutic agents. A knowledge of the pathological possibilities of the infection is one of the factors on which we base our prognosis.

**The Wassermann Reaction as a Guide in Prognosis.** In the vast majority of cases of syphilis a close correlation exists between the signs and symptoms of the disease and the complement-fixation test. Experience has taught us, however, to modify some of the views originally held. We should not, however, emphasize the exceptional and incidental phases of the reaction and forget the rule which generally holds good.

The report of cases of neurosyphilis in which negative findings were present in the spinal fluid with positive signs or symptoms of the central nervous disease, and conversely, cases with positive findings in the fluid and no symptoms is of much value in calling attention to exceptional conditions. Such reports are, however, misleading if the impression is conveyed that spinal fluid findings are valueless in the diagnosis and prognosis of neurosyphilis. Paresis in practically 100 per cent of cases has a definite formula in the fluid. The absence of the paretic gold-sol curve enables us to exclude paresis in our prognosis. The majority of active progressive tabetics have definite fluid changes which are of prognostic value and an accurate guide to treatment.

Some years ago a repeated negative reaction in the blood was looked upon as an accurate criterion of cure. We now know that many such patients have a positive reaction in the spinal fluid, while the blood remains persistently negative. Furthermore, a weakly positive reaction in a patient with a definite history of syphilis is an indication for further treatment. A reaction of this kind reported from the laboratory is usually considered a negligible one. Before this interpretation is placed upon it the history of the patient, together with the amount of treatment he has received, should be carefully considered. In expressing an opinion, therefore, regarding the question of cure, or the absence of a syphilitic infection, the Wassermann reaction of the blood, as well as of the spinal fluid, should be carefully correlated with the previous history of the patient. I have often been aided in my interpretation of a Wassermann reaction by opinions from my colleagues as to the

clinical findings which are present. In several cases an eyeground examination has shown the existence of vascular disease with degenerative changes in the presence of a negative blood. In some cases the vascular degeneration is a progressive one and may be met with in the early stages of syphilis. It would, therefore, be fatal to such patients to state that the syphilitic infection has been cured. It is in cases like these, and similar ones with localized lesions, that we obtain a negative reaction in the presence of active disease. Some of these patients two or three years later may show evidence of hypertension and it is a question whether all syphilitics should not be under observation from time to time for a cardiac and ophthalmological examination and whether our intensive arsphenamine-mercury treatment should not be followed up by iodides.

The possibilities of error in the interpretation of the Wassermann reaction are more numerous on the negative than on the positive side and we might briefly formulate them as follows: The blood is negative in about 6 per cent of late active cutaneous syphilis and sometimes in early malignant syphilis; in a certain percentage of cases with cardiovascular syphilis; in certain localized progressive vascular affections of the eye; occasionally in congenital syphilis although the infant has clinical signs of the disease. The blood usually becomes strongly positive after treatment.

In the following types of neurosyphilis the spinal fluid is often negative and the blood may be negative or positive; in vascular neurosyphilis; in abortive tabes and the late degenerative stages of the disease and sometimes in the terminal stages of paresis. Epilepsy, cerebral gumma and syphilitic psychoses are also usually accompanied by a negative Wassermann reaction in the fluid.

It is well to keep in mind that the Wassermann reaction has been tested in hundreds of thousands of cases and has stood up better than any other laboratory procedure. It is one of the symptoms of syphilis and like others may occasionally be absent. Not infrequently it is the only symptom of the infection when the lesion producing it cannot be uncovered. It requires confirmation by more than one laboratory together with a review of the patient's general history and a careful consideration of the theoretical possibility that other conditions might cause it.

In summarizing one can say with a certain degree of assurance that a persistent positive reaction controlled in several laboratories means active treponemata in some part of the body and is an indication for treatment. Autopsy findings in cases with a history of syphilis who have died from some intercurrent affection show that in over 90 per cent the aorta is the site of a lesion and that in over 40 per cent there is involvement of the viscera.

A persistent negative reaction in the blood and spinal fluid after intensive treatment is an indication of cure in the great majority of cases. The cured cases of syphilis do not go to autopsy

and this statement is not susceptible of pathological proof; but the subsequent histories of these patients with their marital history and healthy children support this view. The exceptional cases on the negative side which have been referred to cannot take away from the value of a negative Wassermann reaction and neither can they be accepted as proof that syphilis is an incurable disease.

Modern treatment is without doubt more effective in curing the disease than before the introduction of the arsenic compounds and the more systematic and better methods of employing mercurials. It is generally conceded that treatment begun at the earliest possible time before the development of a positive Wassermann reaction offers the best hope of aborting the infection. Opportunities for employing abortive treatment are often missed by failure to diagnose extragenital chancres, atypical or insignificant looking lesions and so-called mixed sores. In women the primary sore is seldom seen and here, as well as in the infections which take place at the time of conception and during pregnancy, the favorable time for abortive treatment is long passed before specific remedies can be employed. In the large group of cases of congenital and antenatal syphilis the ignored infection overwhelms the victim before therapeutic help is possible or of much avail. It has been estimated that in 70 per cent of all cases of syphilis treatment is not begun until the stage of generalization is well advanced. The ideal time for abortive treatment is often missed by conditions beyond our control. In cases where the primary sore is evident, the lack of clinical knowledge and inability to properly employ the dark-field microscope leads often to loss of valuable time. Failure to demonstrate the treponemata in the chancre may be rewarded by success in the fluid aspirated from the communicating lymph node. More careful and detailed instruction is necessary in our medical schools in the diagnosis of the objective appearance of the primary sore as well as in the employment of the dark-field microscope. The average time for the Wassermann reaction to appear in the blood should always be kept in mind as many mistaken diagnoses are made by blindly following the laboratory reports without proper correlation with the clinical picture. Clinical experience has amply demonstrated that abortive treatment is successful at this stage of the infection even though animal experiments have shown a diffusion of the organism beyond the site of the primary sore and its lymphatic connection. We now know that immunity to a new infection in syphilis means that the body still harbors the parasite and in this respect differs from the bacterial diseases which confer a life-long immunity and in which the causal agent disappears. A reinfection in syphilis assumes the complete disappearance of the treponemata and their protective power against a new invasion. Definite proof as to the curability of syphilis is therefore supplied by cases of reinfection which are becoming more and more numerous

as we are becoming more expert in diagnosis and in handling our specific drugs. The following cases which among others have come under the writer's observation are cited as illustrations:

P. P., a male, aged thirty-one years, had a penile chancre in November, 1918. He was admitted to the clinic with mucous patches in January, 1919. The Wassermann was 4 plus. The treatment consisted of 25 injections of arsphenamine and 13 of mercury salicylate. The Wassermann on three different occasions was negative, the last in September, 1919. He then disappeared and was not seen again until September 15, 1920, when he returned with an indurated sore in the sulcus of the penis of two weeks' duration. The dark field showed many treponemata. Wassermann 4 plus. Exposure was admitted.

D. S., a male, aged twenty-five years, came to the clinic in August, 1920, with a chancre of the penis and inguinal adenopathy. Dark-field examination, positive; Wassermann reaction, negative; no skin or mucous membrane lesions. Treatment was begun immediately. Blood a week later was reported strongly positive. He received 16 injections of arsphenamine and 22 of mercury salicylate in two courses. A spinal fluid examination made after the first course was negative in all phases. The blood, which was also negative at this time, was tested at regular intervals and continued negative, the last examination being made on January 5, 1922.

On February 15, 1922, the patient consulted us for a superficial clean-cut lesion on the shaft of the penis opposite to his previous ulceration and of four or five days' duration. He admitted exposure four weeks previously. The dark field showed numerous treponemata. Wassermann, negative; no glandular enlargement; no cutaneous or mucous membrane lesions. To determine whether this was a true reinfection, saline dressings only were ordered and he was again examined on February 21, when the lymph nodes on the side of the lesion were found to be distinctly palpable and fluid aspirated from one of them contained many treponemata. The Wassermann continued negative until February 28, when it was reported +. The epitrochlear glands were now slightly enlarged. Saline dressings were continued. On March 6 the blood was ++++ and on March 14 a typical secondary maculopapular eruption made its appearance on the trunk.

It is neither expedient nor desirable to subject our supposedly cured cases to the rigid test of cure, namely, a new infection, so we are obliged to rely on a persistent negative Wassermann reaction in the blood and spinal fluid, a long absence of signs and symptoms and the revelations of matrimony with its resulting progeny.

Every practitioner who has followed the life history of infected individuals knows that many die in advanced life from diseases other than syphilis even with a persistent positive Wassermann reaction. I am familiar with a man almost eighty years of age with a positive reaction due to a syphilitic infection over fifty years ago. He is in excellent health and appears much younger than his years. He has no subjective or objective evidence of his old infection. A condition of perfect parasitism has become established between the organism and the host so that they now dwell together in peace and harmony. Time and antibody formation in certain cases gradually weaken the virus and fibrosis obliterates the activity of focal lesions in organs with a large margin of safety.

Marriages and healthy children are met with in individuals with persistent positive Wassermann reactions. A focal lesion in the tongue existed for years in a man who came under my care, the result of an infection years before he married. His wife gave birth to several healthy children and all were negative to the Wassermann reaction. We frequently see men and women with late syphilis of the skin the parents of healthy children. It is not always good judgment to withhold our consent to matrimony in individuals years after infection whose reaction persists after prolonged treatment. The world contains many robust individuals born of parents previously syphilitic. The late lesions of syphilis are often localized. Their carriers neither convey nor transmit the disease.

Syphilis is a disease of so many contradictions and exceptions that the foregoing statement must be accepted with reservations. They may be the exceptions which prove the rule, but they should dissipate a part of the pessimism as to possibility of cure which depresses the victim and impairs the physician's will to cure. Clinical medicine is a vast workshop in which experimentation, observation and interpretation yield results as important to our art as the findings in the purely experimental laboratory. Each must control the work of the other but neither must assume an attitude of intolerance. The problems of syphilis appeal to the clinician in every field of medicine and equally to the laboratory worker. With a proved etiology, accurate methods of diagnosis, specific drugs and a fairly accurate measure of their effects the practical application of this knowledge should lead to a large percentage of cures.

It is safe to state that the problem of cure is approached by the majority of practitioners with little exact knowledge of the pathology of the disease and with less knowledge as to the employment of the specific drugs. The early stage of neurosyphilis is often entirely overlooked and not considered in its relation to the late degenerations; vascular and eye lesions are ignored until irreparable damage is done. A cure is supposed to follow the administration

of a definite number of intravenous injections of arsphenamine with solutions improperly prepared and crudely given. If cure does not result the patient is at fault and the doctor holds himself blameless. Under these conditions complete clinical and serological cures are the exception rather than the rule and the defensive forces of the body weakened by insufficient treatment permit foci to develop in the central nervous system and elsewhere. Insufficient and improperly employed therapeutics is often more harmful than helpful and may precipitate in an early period lesions usually seen late in the infection. If we admit the increased incidence of neurosyphilis since the arsphenamine era its explanation is to be found in insufficient early treatment and in the routine administration of so many doses of arsenic and so much mercury regardless of the individual's requirements.

Observations and analysis of cases over a period of years that were properly treated has failed to convince me that neurosyphilis has been rendered more frequent by the modern method of treatment. In the early days of arsphenamine administration when a few doses of the drug were considered the maximum requirements the incidence of neurosyphilis may have been more frequent. British observers have remarked an increase in neurosyphilis among cases treated in the army where a fixed number of injections were given to cure the existing lesions and return the man to active duty at the earliest possible time; a symptomatic cure only was attempted. Since we have insisted on an examination of the spinal fluid before a final pronouncement of cure and proper treatment of a pathological condition, if present, we have had no case of early syphilis return to us with the so-called neuro-recidives. In other words, if the central nervous system is not involved early in the infection, it is highly improbable that it will be implicated later. If it is found to be involved in the early period during active treatment and fails to yield to additional treatment along the usual lines it will yield to intraspinal injections. The lesson to be learned from the discussion as to the increased incidence of neurosyphilis and the weakening of the antibody defence by modern treatment is to give the remedies in suitable doses at proper intervals and over a sufficiently long time to destroy all the invading organisms. Too long rest periods between courses of treatment permit the surviving treponemata to begin anew their activities. Neurosyphilis may show an increased incidence in cases improperly treated. It has, however, always existed and its frequency has been brought to the foreground by our modern methods of investigation and the attention which has been focussed on it.

We can speak with a certain amount of assurance as to the prognosis of cases of early syphilis if coöperation is brought about between the physician familiar with the possibilities of the disease,



modern therapeutic methods and a patient with ordinary intelligence. The future of such patients depends on careful supervision over a period of years. A control of treatment by the Wassermann reaction in the blood as well as the knowledge gained by lumbar puncture are imperative.

Attention focussed entirely on the reaction of the blood with neglect of the spinal fluid has in many cases led to disastrous consequences and irreparable conditions. A patient discharged after adequate treatment with a conservative opinion as to the cure with a persistent negative blood and negative fluid has up to this time never returned with clinical or serological evidence of neurosyphilis. On the contrary, we have many records of patients discharged with a negative blood only who have come back to us after months or years with definite evidence of nervous system involvement. The prognosis of early syphilis is therefore intimately related to the cyto-biological changes in the fluid as well as the Wassermann reaction in the blood. The development of persistent hypertension in these cases after what is considered adequate treatment is another condition which demands further study. It is an occasional sequence of the infection in young adults where the usual factors cannot be invoked as a cause and may be looked upon rather as a coincidence than the result of the infection or treatment employed. Progressive low grade reactions may continue in the heart and arteries with a negative Wassermann. Possible toxic effects on the bloodvessels by arsenic should be kept in mind. It may be advisable in these cases to ignore the reaction and to follow up the usual treatment with the iodides combined with mercury in moderate doses. We are, as the result of experience, adding something to the credit side of our diagnostic and therapeutic methods and thus increasing the patient's chances of cure.

We are yet far from a standardized and ideal formula of treatment which insures the patient's future and eliminates the possible harmful effects of the drugs. In this connection a reference to the occurrence of jaundice during and after arsphenamine treatment may not be inopportune. In our endeavor to sterilize the patient rapidly the tendency is to increase the number of arsphenamine injections in our so-called course of treatment and to give additional courses. If we keep in mind the fact that after each dose of the drug a certain percentage is stored in the liver and with frequent repetitions a toxic amount may be retained, it is not difficult to grasp the relationship of the drug to the jaundice and the degenerative changes in the liver.

In my own work jaundice has appeared from a few days or weeks to three and a half months after the last dose of arsphenamine and not infrequently in groups. We have seen it after all the arsphenamine preparations, including silver arsphenamine.

Its development can sometimes be foreseen by the occurrence of certain symptoms such as severe pains in the arms and legs, lassitude and loss of appetite several weeks before the onset of the jaundice.

The incidence of other by-effects of our drugs, such as types of dermatitis, purpura, severe anemia and encephalitis hemorrhagica, while rare must also be considered in our general scheme of prognosis. While millions of doses of arsenic preparations have been administered with no untoward results, many deaths from arsphenamine have been unrecorded and too little emphasis placed on its toxic and by-effects. More technical knowledge and skill are required in our modern treatment as the possibilities of accidents are greatly increased.

The prognosis of late syphilis is a vastly more complicated problem than in early syphilis. It is concerned with phases of the disease in which damage may have resulted in organs essential to life and in individuals with the degenerations incident to age. Brain hemorrhages, thrombosis and aneurysms occur in advanced arterial disease where the specific factor is reinforced with the mechanical factor of the circulation. Changes in the heart muscle resulting in fibrosis and in the coronary arteries causing deficient blood supply to the heart may be modified but not cured by our specific drugs. Great harm may follow their indiscriminate and careless employment. A possible Herxheimer reaction in lesions involving important organs may cause alarming symptoms and even death. Where the possibility can be foreseen careful preliminary treatment must be employed. The internist and the syphilographer must work hand in hand in planning the best therapeutic procedure in cardiovascular and visceral syphilis as only in this way can possible accidents be prevented and the interest of the patient best conserved.

When the stigmata of paresis appear a deep and disseminated encephalitis is present from long continued and progressive changes in the small vessels of the brain. The brain cells are atrophic as a result of the diminished blood supply and the possible toxic effects of the treponemata. We can only offer a hopeless prognosis in spite of all the procedures that have been advocated and employed. In certain stages of paresis with marked meningeal changes as shown in the fluid formula a decided temporary improvement and apparent arrest of the process can be effected by intensive intravenous and intraspinal treatment. The meningitis and superficial lesions in the cortex are reached by the remedies. The deeper lesions remain quiescent for a time and again become active. Patients die with advanced brain atrophy with little or no evidence of meningitis. The chances of arresting the pathological process in tabes are much greater than in paresis. The treponemata are more accessible to our drugs as the secondary degenerations prob-

ably originate from a meningitis about the posterior nerve roots. A progressive tabes shows in the fluid the cytology of a meningitis. The process has in many cases been permanently arrested by combined intravenous and intraspinal medication. It is useless in advanced degenerations with little or no evidence of a meningitis. I have in no manner changed my opinion as to the great value of properly employed intraspinal medication in properly selected cases in spite of the theoretical objections that have been advanced by its opponents. Cases treated years ago have returned for control observation and puncture. Their fluid findings continue negative and no clinical signs point to progress in their cord degeneration. The method has stood the test of time and is a valuable adjunct to our therapeutic measures. It is well to again emphasize the relationship of the fluid findings in early syphilis to these late degenerations. If recognized early and properly treated both tabes and paresis will theoretically cease to exist. The neurologist sees the end-stages of tabes and paresis and pronounces them incurable; the syphilologist should recognize their early beginnings and cure them. Ability to visualize the pathological changes in syphilis from the primary sore to the dissolution of the most specialized and highest brain centers gives one much respect for the possibilities of the invading organism. In prognosticating the fate of the infected individual the defensive forces of the body should always be kept in mind. Every syphilitic is not a potential paretic or tabetic; neither must he necessarily die from the cardiovascular phase of his infection.

From the experimental view point we know little of the defensive forces of the body with the exception of the fibrosis which localizes and extinguishes the focal lesions and the attenuation of the virulence of the infectious agent by time. The usual immunizing substances cannot be demonstrated in syphilitic blood or tissues. Spontaneous cure may, however, occur in syphilis without treatment and many cures followed treatment in the pre-arsphenamine era by methods now regarded as inefficient.

In congenital syphilis the result of recent infection in the parent, early abortion in the first pregnancy is followed by a syphilitic child born at term and later by children who are born apparently healthy but who develop interstitial keratitis or other phases of late congenital syphilis.

In these cases which give us a clinical demonstration of an attenuation of the virus we must assume that the mother develops antibodies which are transmitted to her child with the organisms of the disease. In prognosticating the future of the syphilitic child one should therefore regard the age of the infection in the parents. Children born of parents who acquired the infection several years before marriage may escape it entirely but many such children who present a perfect physical condition on investi-

gation will be found to have positive Wassermann reactions. I have in mind a man who married eight years after his infection—who received what at that time was considered adequate treatment. He consulted me for a sudden deafness in his four-year old child. Both the blood and spinal fluid showed positive Wassermann reactions. A six-year old daughter also had a 4 plus reaction in the blood, the cause of which was not revealed by examination. Both the children were well developed mentally and physically. The existence of the infection would not have been suspected had it not been for the sudden onset of the eighth nerve involvement.

From observations of cases like these, which are not unusual, it would seem advisable to restudy the entire subject of congenital syphilis and to carefully control the possibility of the disease by serological tests at various times after birth. We are at present treating at the Vanderbilt Clinic a large number of congenital syphilitic infants and, where possible, investigating their spinal fluids. This is done usually after treatment and our statistics, while not yet tabulated, give the impression of a similar incidence of involvement as in the adult. We have obtained results in these infants by intramuscular injections of mercury and neoarsphenamine, which are encouraging both as to the clinical manifestations and the blood reactions, and feel that we can offer a more hopeful prognosis than by the use of mercury internally or by inunction. It is not yet possible to say how much, if at all, we can influence the nervous system involvement by the method in question. Intraspinal treatment in the small patients has not yet been attempted by us because of the technical difficulties and the possibility of damage to the delicate structures of the infant. We shall probably see the usual number of cases of juvenile tabes, paresis or other types of neurosyphilis as in the adult whose early neurosyphilis has been overlooked or treated improperly.

The later phases of congenital syphilis, such as interstitial keratitis, yield much more rapidly to arsphenamine than to mercury and cease to relapse when the blood reaction becomes negative.

It is possible in many cases of congenital syphilis by persistent and well directed treatment to change what was considered a Wassermann fast reaction.

In acquired syphilis many cases are met with which give a persistent and strongly positive Wassermann reaction with and without clinical symptoms. In 90 per cent of these cases which came to autopsy at the City Hospital the aortic walls showed focal and advanced lesions of syphilis. In some of the cases the physical signs of aortic disease were not present during life. Warthin's observations that all syphilitic patients who come to autopsy have small focal lesions in the heart, muscle or viscera explains many of the mysteries of the so-called Wassermann fast cases. The lesions are often too small to cause symptoms and the diagnostic skill of the clinician cannot uncover them. A persistent Wasser-

mann reaction in the blood or one which disappears under treatment and slowly returns during rest periods may be due to reinfection of the blood from the central nervous system. I have met with instances of this kind where the reaction disappeared permanently after intraspinal treatment of a neurosyphilis. The majority of persistent reactions can be altered by their interpretation and properly directed treatment. In paresis we have an example of what may properly be termed a Wassermann fast reaction in the spinal fluid. It persists during years of intensive treatment. The blood Wassermann may be modified but in the fluid seldom or never. Frequent changes in this reaction in the fluid in well developed cases of neurosyphilis we seldom see. In types of early syphilitic meningitis we have exceptionally met with these fluctuations. In curable cases of neurosyphilis the various phases of the fluid yield in regular order and gradually, and not by up and down gradations.

In discussing some of the factors which bear on the prognosis of syphilis I have endeavored to show that the infection in the late stages may be localized in organs with a large margin of safety or in tissues whose impairment does not endanger life. Late lesions in the skin may exist and recur for years with no impairment of the general health. The small visceral lesions described by Warthin are met with in organs which may withstand for years their slow progression and ultimately fibrosis may end their activity. These favorable factors should not be overlooked nor should they lead us to minimize the effects of the disease when it involves the heart, the large vessels, the nervous system and the eye.

The individual syphilitic should be regarded as a potential candidate for the more serious phases of the infection and should be safe guarded as far as our modern diagnostic and therapeutic measures are available. The majority of the intelligent class of patients will coöperate with the physician who handles them tactfully and informs them of the reason for each procedure. The results of treatment and the justification of a favorable prognosis rests mutually on the physician and the patient.

**Summary.** In summarizing we might say the future of the syphilitic patient depends upon the knowledge and training of the physician first consulted. If familiar with modern diagnostic methods he will not neglect the employment of the dark-field microscope. A search for the treponemata may be rewarded by an examination of the fluid aspirated from the communicating lymph nodes after failure to demonstrate the organism in the primary sore. When the diagnosis is made the physician should impress the patient with the necessity for vigorous and thorough modern treatment and endeavor to make him appreciate the seriousness of the disease.

Mercury by mouth is a desultory way is of no value in aborting the infection. Many patients receive insufficient treatment

because physicians have not acquired accurate knowledge of the modern specific drugs and are ignorant of their proper administration. This criticism is as valid now with our greater knowledge as formerly before our modern studies of the disease. The fault today lies not only in the lack of training on the part of the physician but also in his failure to impress the patient with the necessity of continuing treatment long after the symptoms have disappeared. All physicians treating syphilis should have a thorough knowledge of the pathology of the disease and its possibilities in the early as well as the late stages.

In the primary stage, before the Wassermann reaction becomes positive a cure generally may be assured by intensive treatment. At least two courses of 8 doses each of arsphenamine and two courses of 15 injections each of mercury should be given. Continued observation and control by the Wassermann test and lumbar puncture are necessary as in the treatment of later stages.

In the secondary stage, after the Wassermann reaction has become positive, a cure is not so readily obtained but is possible if treatment is thorough and not stopped as soon as the blood becomes negative. The positive reaction continues as a rule for some time after all the other symptoms have disappeared. Depending on the length of time the blood has been positive, patients should receive from two to three courses of arsphenamine and three or more courses of mercury. If the spinal fluid is positive, more treatment may be required, including intraspinal injections. Cure should be pronounced only after a long period of observation. A guarded prognosis should be given when the disease has progressed beyond the early secondary stage.

A symptomatic cure is possible in latent and tertiary stages if adequate treatment has been given, even in so-called "Wassermann-fast" cases. Adequate treatment means the administration of not less than two to four courses of arsphenamine combined with and followed by mercury, iodides and mixed treatment. In the so-called "Wassermann-fast" cases an examination of the spinal fluid is imperative.

The prognosis is not favorable in certain types of neurosyphilis. This statement applies especially to the degenerative stages of tabes and paresis. It is, however, possible to anticipate and arrest the progress of early active tabes and paresis. The majority of cases do not respond to treatment as ordinarily administered. Early cases of neurosyphilis which do not respond to intravenous treatment combined with mercury are generally cured by intraspinal treatment. Paresis and tabes result from neurosyphilis improperly treated in the early stages.

In congenital syphilis, with the old methods of treatment it was impossible to obtain a negative Wassermann reaction and even now the prognosis is not as favorable as in the acquired disease because of the severity of the infection, interference in the develop-

ment of the growing tissues and the difficulty of carrying out the treatment.

In congenital syphilis with involvement of the central nervous system, because of the technical difficulties in treatment the prognosis is less favorable than in the similar type of syphilis in adults.

It is frequently necessary to give a prognosis because of contemplated matrimony. While a rigid standard cannot be maintained physicians should endeavor to obtain a negative Wassermann reaction in the blood for one or two years after adequate treatment, with a negative spinal fluid, before giving consent. The patient should remain under observation for several years. If the patient be a woman with a positive Wassermann reaction treatment should be begun during early pregnancy and continued throughout.

Marriage may be permissible in spite of a positive blood Wassermann if thorough treatment has been administered. In exceptional cases after prolonged treatment and after the expiration of at least five years from the time of the infection and two years' freedom from all symptoms, a conditional consent to matrimony may be given.

The marriage of heredo-syphilitics with the disease still active is not desirable, even though the danger of transmission of infection to the third generation is negligible.

We must remember that untreated or imperfectly treated syphilis is essentially a relapsing disease. In thoroughly treated cases, however, the prognosis is favorable.

The modern criteria of cure are dependent on: (1) Adequate treatment; (2) a negative Wassermann reaction, for at least a year after cessation of all treatment, which continues negative after a provocative injection of arsphenamine; (3) a negative spinal fluid; (4) negative findings in the cardiovascular system. The early involvement of the cardiovascular apparatus may be followed by changes in the heart and aorta with a negative Wassermann reaction.

In this paper, which is more or less fragmentary and incomplete, many factors which influence the prognosis of syphilis have not been touched upon. I would like to suggest to those who treat syphilis to acquaint themselves more accurately with the possible toxic effects of the modern arsenicals. Has the hypertension which is at times met with after prolonged treatment any relation to the known toxic action of arsenic on the bloodvessels? How long is arsenic stored in the liver after the cessation of our usual courses of the drug? Can jaundice be prevented by a low protein diet during treatment? Is the elimination of arsenic hastened by the simultaneous use of the iodides? To what extent do our various methods of giving arsphenamine develop arsenic-fast strains of the *treponemata* and thus render our further therapeutic attacks less efficient?

## THE HEMOLYTOPOIETIC SYSTEM IN THE PRIMARY ANEMIAS, WITH A FURTHER NOTE ON THE VALUE OF SPLENECTOMY.<sup>1,2</sup>

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It is convenient and desirable, from a practical point of view, to consider all diseases of the blood, but especially the so-called "primary anemias," from the dynamic standpoint of the constant interplay of the blood-forming and blood-destroying apparatus (which may be termed the hemolytopoietic system and the adjustment thereof spoken of as the hemolytopoietic balance). By using the various diagnostic measures now available there can thus be determined not only the actual disease in question, but whether it is chiefly due to an excess of blood destruction or to a paucity of blood formation; and in the individual case, how grave a disturbance of this hemolytopoietic balance exists and whether it is becoming more or less upset.

**Hemolytopoietic Balance.** A correct estimation of the condition of this mechanism at a given moment (practically the hemato-poietic-hemolytic index of Schneider<sup>3</sup>) is rendered difficult, both by the semiquantitative nature of some of the tests required and by the complexity of the system itself. To discuss the latter point first, a steadily accumulating mass of evidence is forcing us to recognize that bone-marrow, lymph nodes, spleen, liver and the whole "reticulo-endothelial apparatus"<sup>4</sup> must be considered as definite a mechanism for the control of the cellular elements of the blood as the digestive or endocrine systems are in their respective spheres. As with the latter system, the complexity of the problem is made more acute by the marked (and as yet imper-

<sup>1</sup> Read before the New York Academy of Medicine, January 18, 1923, and in abstract before the Association of American Physicians, May 1, 1923.

<sup>2</sup> The "hemopoietic system," as it has been loosely designated, is not a desirable term, as it ignores the blood-destroying mechanism, which is at least of equal importance with that of blood formation. Custom has long sanctioned the use of "hemo" rather than "hemato," in the compound word.

<sup>3</sup> *Journal-Lancet*, 1917, 37, 105; *Arch. Int. Med.*, 1916, 17, 32; *ibid.*, 1917, 19, 156.

<sup>4</sup> By "reticulo-endothelial apparatus" is meant the widespread cells of reticular or endothelial origin that possess marked capacity for phagocytosis of foreign bodies, body cells, bacteria, etc. They are similar to or identical with the macrophages of Metchnikoff, klastmatocytes of Ranvier, adventitia cells of Marchand, resting wandering cells of Maximow, pyrrhol cells of Goldmann, endothelial leukocytes of Mallory, histiocytes of Aschoff. Jaffé (*Wien. klin. Wehnschr.*, 1922, 35, 595) has shown that they are functionally significant as the Kupffer cells of the liver, the pulp cells (splenocytes of the spleen in the endothelium of spleen, lymph nodes, bone-marrow and adrenal and reticulum of spleen, lymph nodes and bone-marrow.)



fectly delimited) ability of one member of the system to take over, in times of stress, functions belonging primarily to some other member of the group. Thus, where blood destruction is greatly increased (as in hemosiderosis, some cases of pernicious anemia and chronic malaria) or in experimental plethora,<sup>5</sup> or after the administration of hemolytic immune serum,<sup>6</sup> the products of blood destruction are found in Kupffer cells, lymph nodes and bone-marrow (parts that ordinarily are not noticeably concerned in this process) in much larger quantities than in other parts of the body. The quick response of the normal bone-marrow to demands for more blood cells is well known, but, in addition, if sufficiently intense and protracted strain is put upon the blood-forming apparatus, it is not infrequent to find other members of the hemolytopoietic system reverting to their embryonal functions or metaplastically taking on myeloid activity;<sup>7</sup> and even in a case I recently reported, the bone-marrow assumed definite lymphopoiesis.<sup>8</sup> By quite similar reasoning is to be explained the adjustment that follows splenectomy in normal individuals, whereby after a relatively short period of time the splenectomized patient or animal returns practically to normal in most or all hematological details.

**Methods Available.** Reverting to what I have spoken of as the semiquantitative nature of some of the tests involved, I would like to review what evidence may be obtained toward estimating the amount of blood-cell formation and destruction. Although this involves statements that are far from new, I hope that the repetition will be pardoned, in view of the fact that apparently in few clinical laboratories or in few reported cases in the literature has full advantage been taken of available methods.

On the side of blood destruction is the evidence to be obtained from the appearance of the erythrocytes when vitally stained or in stained spreads, and, more directly, from the urobilin output in feces or duodenal contents. According to current views,<sup>9</sup> erythrocyte destruction begins while the cells are still in the circulation. By a process of fragmentation they become smaller and smaller until the disintegrated products are taken up as hemoglobin-bearing dust chiefly by the spleen, to be turned over to the liver by steps that we know little about, there to be excreted

<sup>5</sup> Krumbhaar, E. B., and Chanutin, A.: *Jour. Exp. Med.*, 1922, 35, 8427.

<sup>6</sup> Pearce, R. M., Krumbhaar, E. B., Frazier, C. H.: *The Spleen and Anemia*, Lippincott, 1917, p. 189.

<sup>7</sup> Donhauser, J. L.: *Bull. Ayer Clin. Lab.*, 1908, 5, 46. Bunting, C. H.: *Jour. Exper. Med.*, 1906, 7, 365. Dominici: *Arch. de méd. expér. et d'anat. path.*, 1901, 13, 1. Domarus: *Arch. exp. Path. u. Phar.*, 1908, 58, 319. Tanaka: *Ziegler's Beitr.*, 1912, 53, 388 (Lit.).

<sup>8</sup> Krumbhaar, E. B.: *Jour. Med. Research*, 1922, 43, 369.

<sup>9</sup> Rous, P., and Robertson, O. H.: *Jour. Exper. Med.*, 1917, 25, 651 and 665.

# 1. BONE MARROW

FORMS ERYTHROCYTE AND GRANULOCYTE SERIES AND PLATELETS  
AIDS IN BLOOD CELL DESTRUCTION THROUGH NO. 5

## 5. RETICULO ENDOTHELIAL

### SYSTEM

(KUPFFER CELLS OF LIVER; SPLENOCYTES  
 MACROPHAGES, ENDOTHELIAL CELLS, ETC.)  
 ESPECIALLY IN THE SPLEEN, LIVER, BONE  
 MARROW, LYMPH NODES, LUNGS, ADRENALS.  
FORMS LARGE MONONUCLEAR AND "TRANSI-  
TIONAL" GROUP OF BLOOD CELLS  
AIDS IN DESTRUCTION BY PHAGOCYTOSIS OF  
CELLS OR PIGMENT, ESPECIALLY IF CELLS  
ARE BEING DESTROYED IN LARGE NUMBERS.

## 2. SPLEEN

FORMS BLOOD CELLS IN EMBRYO MAY  
REVERT TO THIS FUNCTION IN ADULT.  
HORMONE STIMULATING BONE MARROW  
AIDS IN BLOOD DESTRUCTION THROUGH  
NO. 5 (PERHAPS ALSO BY PREPARING  
EFFETE CELLS FOR DESTRUCTION IN  
THE LIVER.)

## 4. LYMPHOID TISSUE

FORMS LYMPHOCYTES  
AIDS IN DESTRUCTION THROUGH NO. 5

## 3. LIVER

FORMS BLOOD CELLS IN EMBRYO. MAY REVERT TO  
THIS FUNCTION IN ADULT.  
AIDS IN DESTRUCTION THROUGH NO. 5 (KUPFFER)  
ELIMINATES HEMOGLOBIN PIGMENT AS BILIRUBIN,  
CONSERVING THE IRON MOIETY.

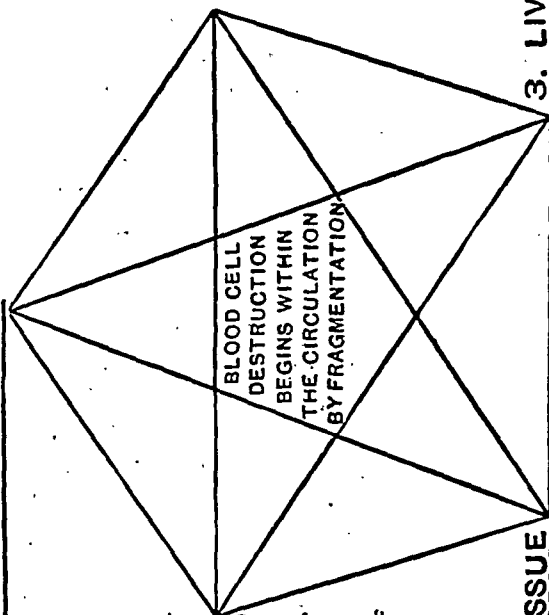


FIG. 1. HEMOLYTO-POIETIC SYSTEM

as bile pigment with conservation of the iron fraction. Microcytes, therefore, in the peripheral blood, and poikilocytes as well, are to be taken as evidence of increased blood destruction. This has clinical confirmation in hemolytic jaundice—the disease *par excellence* of excessive blood destruction, where microcytes are notoriously numerous. However, Price-Jones<sup>10</sup> has recently showed that whereas in pernicious anemia the average size of the red cell is greater than normal, after hemorrhage it is smaller than normal—a sign, therefore, of deficient blood formation. The degenerated “stippled” erythrocytes of lead poisoning are not within the scope of this paper.

The urobilin output should give us direct evidence of the amount of blood destruction, but unfortunately hitherto unsurmountable difficulties leave this still as a semiquantitative test only. If the original technic of Wilbur and Addis<sup>11</sup> is followed, not only is the test a fairly lengthy one, but the unknown factor of the amount of urobilin absorbed by the intestine cannot be accounted for. In Schneider's<sup>12</sup> method of using a sample of duodenal juice, normal fluctuations of output, as well as obvious difficulties in collecting a valid sample, present to my mind even greater handicaps. In addition, there has been no standardization of several factors such as intensity of light, width of column of fluid and other details which may seriously affect the reported result; and in Todd's book, *Clinical Diagnosis* (1919), and Haden's *Clinical Laboratory Methods* (1923), the only text-books I can find in which the test is mentioned at all, calculations apparently give a result ten times greater than Wilbur and Addis intended.\* This state of affairs is so regrettable that work is now going on in our laboratories to make this test serviceable by eliminating preventable errors. Fortunately, the different results obtained in hyperhemolysis or hypopoiesis (as compared with the normal) are so great that, in spite of the difficulties first referred to, I am confident the test will prove to be of sufficient value to be used in every carefully studied case of anemia.

On the side of blood formation, information can be obtained from the blood counts (hemoglobin, erythrocytes, leukocytes, platelets), especially if frequently repeated accounts are made; but care should be taken not to place reliance on variations so slight that they are within the limits of observational error. The less constant the conditions attending the various tests and the less your acquaintance with the source of the report the greater should be your conservatism in this respect. Especially valuable information may be obtained from a properly prepared vital or stained spread. Nucleated forms are a sure indication of bone-

<sup>10</sup> Jour. Path. and Bacteriol., 1922, 25, 487.

<sup>11</sup> Arch. Int. Med., 1914, 13, 235.

<sup>12</sup> Loc. cit.

\* Details of Giffin's modification of the method of performing the test on the duodenal contents can be found in Simon's *Clinical Diagnosis*, 10th ed., p. 347.

marrow activity, and quantitative comparisons may, therefore, be used to estimate roughly both the stress of the demand and the ability to supply. The normoblast may appear in any severe anemia; the megaloblast, or earlier form, is more rarely found, except in pernicious anemia, where it possesses diagnostic value. Nuclear remnants, Heinz bodies, Howell-Jolly bodies and Cabot rings are similar signs of bone-marrow activity. In terminal conditions, however, many and bizarre nucleated forms may appear in the blood streams without finding any bone-marrow hyperplasia at autopsy. The size and shape of the erythrocytes have been already referred to; numerous macrocytes, presumably coming from megaloblasts, suggest pernicious anemia. Extensive polychromatophilia (young erythrocytes) also indicates bone-marrow activity, though this is better brought out by the special search for reticulocytes in "vital spreads."<sup>13</sup> Like the urobilin test, this simple test deserves much more frequent use than has yet been accorded it. It is not only a sensitive method of ascertaining and following the bone-marrow activity in a given case, but in hemolytic jaundice, where for some unexplained reason there is a marked reticulosis, it assumes diagnostic value. The shower of nucleated forms and increased number of reticulocytes and platelets in pernicious anemia following splenectomy and at the beginning of a remission are both well-known phenomena.

Finally, the test for the resistance of erythrocytes to hypotonic salt solution<sup>14</sup> determines this phase of blood-cell formation and indirectly throws light on the diagnosis and severity of the process. In hemolytic jaundice, essentially a disturbance in the resistance of the erythrocytes, this test is pathognomonic.

**Results of Treatment.** Treatment of any anemia is naturally directed toward relieving the anemia and removing the cause. The best methods of securing the former of these factors cannot be discussed here, while the attainment of the latter is obviously apparent in secondary anemias. It is in the so-called "primary anemias," however, where the causes are unknown, that the most earnest attempts have been made to restore the lost hemolytopoietic balance by direct intervention with one or other member of the system. Removal of the spleen, one of the chief agents of blood destruction, has proved valuable to a greater or less degree in the several diseases of this group, the value of the procedure always being due to removing one of the chief agents of blood destruction. Although, as is shown in the diagram I have presented, this function can be and is taken over by other members of the hemolytopoietic system it is not exerted to such a great

<sup>13</sup> Vogel, C.: *Arch. Int. Med.*, 1913, 12, 707. Krumbhaar, E. B.: *Jour. Lab. and Clin. Med.*, 1922, 79, 1879, etc.

<sup>14</sup> Pearce, R. M., Krumbhaar, E. B., and Frazier, C. H.: *The Spleen and Anemia*, Lippincott, 1917.

extent for a considerable period, and in some case not ever. According to the doctrine of "hypersplenism," the diseased spleen has developed this function to a pernicious extent, a condition which may not be attained by the other members of the system after splenectomy.

In considering in a more detailed manner the effects of splenectomy in individual diseases, the condition has not materially changed since I last collected reports on this question.<sup>15 16</sup> Nevertheless, by a swing of the pendulum, which is so common in medical advances, splenectomy for pernicious anemia, the most important disease of the group, is now, in my opinion, being neglected just as much as it was being overdone six years ago. The conclusions that were reached at that time have, it seems to me, largely been confirmed by subsequent studies. The operative mortality has been lowered, and most of the survivors have shown marked temporary improvement, the remission usually lasting longer than the average length of natural or post-transfusional remissions. In fact, there is a respectable number of cases that have continued in good health for two to six years after splenectomy. Therefore, my former question, "May it not develop that a larger percentage of such cures (3 in 1200 by the older methods, according to Cabot) will follow splenectomy even though the blood picture does not return absolutely to normal?" can, I think, properly be answered in the affirmative. Of the 208 cases in my list, Giffin reports that 11 of his 53 lived more than three years after operation and 5 still live between four and five years after operation. Of Walterhofer's 16 cases, 1 survived for five years, and 2 more for from two to four years, and so on. This does not mean that every case of pernicious anemia should have the spleen removed or that a cure should ever be hoped for; but it does, to my mind, indicate that in certain cases, especially those that have a relatively recent onset, with a fair blood picture, signs of an enlarged spleen and increased hemolysis, splenectomy is usually advisable. How it should be combined with transfusions is a question that I cannot take up at this time.

In hemolytic jaundice the results of splenectomy continue to be excellent. Although in many cases the resistance of the erythrocytes does not return to normal (indicating that the primary cause of the disease is not in the spleen but probably in the erythrocytes themselves), nevertheless the anemia and jaundice disappear, the urobilin excretion and reticulocyte percentage diminish and the patient is for practical purposes well. If Mayo's caution not to operate during a "crisis of deglobulization" is heeded, the operative mortality may be reduced even below the present rate of 3 per cent.

<sup>15</sup> Krumbhaar, E. B.: *Trans. Coll. Phys., Philadelphia*, 1916, **38**, 158.

<sup>16</sup> Krumbhaar, E. B.: *Pernicious Anemia, Jour. Am. Med. Assn.*, 1916, **67**, 723.

The improvement that has long been known to follow splenectomy in Banti's disease is supported by the later figures. Abdominal adhesions and hemorrhage from varicose veins add to the difficulties of the operation, but marked improvement can be promised to most of the survivors. In fact, many have continued so long without symptoms that they have been reported as cured, but it is unwise to use the term "cure," when the operative procedure has merely removed the chief disturber of the hemolytopoietic balance rather than the cause of the disease itself. I, of course, recognize that as negative methods are the only ones at present available for diagnosing Banti's disease, many cases of splenomegaly due to lues, cirrhosis, portal phlebitis and similar causes are undoubtedly included, and it is especially hard to distinguish them when successful removal of the spleen in the latter group also results in improvement. Nevertheless, the conviction persists that Banti described a primary disease the cause of which is unknown, but which is greatly improved by removal of the spleen.

The most important additions that have been made to our knowledge of this subject in recent years have come from the Mayo Clinic.<sup>17 18</sup> Thanks to them not only have most of our previous opinions been confirmed, but reliable estimates made about the value of splenectomy in newer fields. Thus while leukemia was formerly considered as definitely contraindicated on account of the high operative mortality (see Table), the Mayos have had only 1 postoperative death in 26 cases (much less than in splenic anemia); on the other hand, 15 have subsequently died, so that Giffin considers splenectomy helpful only in a few of the very chronic types of myelogenous leukemia where the organ is fibrous and the leukocyte count never very high. Splenectomy in cases of splenomegaly associated with chronic sepsis has also proved unsatisfactory, both on account of the high operative mortality (20 per cent) and the poor end-result (3 out of 10 survive, and 1 of these is in poor condition). In luetic and malarial splenomegaly not only are the patients' conditions directly improved by removal of the spleen, but they are also usually rendered much more amenable to specific treatment, to which they may previously have proved intractable. In fact, if I may venture an opinion on what is more directly a surgical problem in such secondary splenomegalies, the question being mainly one of operative risk, it would seem desirable to limit the operation to chronic cases that have proved resistant to all other forms of treatment and to proceed with extra conservatism where many adhesions multiply the chances of shock and hemorrhage. For the latest

<sup>17</sup> Mayo, W. J.: Jour. Am. Med. Assn., 1921, **77**, 34.

<sup>18</sup> Giffin, H. Z.: Minnesota Med., 1921, **4**, 132.

brilliant success of splenectomy, namely in the hemorrhagic diatheses, the reader is referred to Brill's communication.

**Summary.** 1. Bone-marrow, spleen, liver, lymph nodes and reticulo-endothelial apparatus combine to regulate the formation and destruction of blood cells in what may be termed the "hemolytopoietic system."

2. The methods for studying the functioning of this system ("hemolytopoietic balance") are discussed.

3. The results of splenectomy in various diseases affecting this balance are presented.

#### RESULTS OF SPLENECTOMY IN MEDICAL DISEASES.\*

Disease.	Number of cases.	Postoperative death (within 1 month).	Postoperative mortality.	Record of subsequent death.	Unimproved.	Improved.	Apparently cured.
Splenic anemia . . .	293	40	13.6	24	4	178	35
Gaucher's disease . . .	16	4	25.0	1	..	9	1
v. Jaksch's disease . . .	19	..	..	1	..	11	1
Hemolytic jaundice . . .	137	4	2.9	..	..	5	125
Pernicious anemia . . .	208	35	16.8	79	26	144	..
Myelogenous leukemia† . .	80	47	56.7	21	2	7	..
Liver cirrhosis . . .	19	6	31.6	5	4	7	..
Luetic splenomegaly . . .	7	1	14.3	..	..	6	..
Tuberculous splenomegaly . .	17	2	11.7	2	1	11	..
Malarial splenomegaly . . .	250	48	19.2	..	..	202	..
Hemorrhagic diathesis . . .	27	2	7.4	..	1	9	15
Total . . . . .	1073	190	17.6	133	38	591	177

† The postoperative mortality in recent reports of this disease is no higher than the average of other diseases of the list.

\* Although larger than any figures heretofore published on this topic, this table by no means attempts to be a complete list. It has been compiled from reports from the following authors:

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## THE CAUSE OF BOTHRIOCEPHALUS ANEMIA. (REPORT OF A CASE.)

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THE broad tape worm, *bothriocephalus latus*, is very commonly encountered in the Baltic provinces of Russia, the Scandinavian countries, and in certain parts of Switzerland. It is the most common tapeworm of China and Japan. The statement<sup>1</sup> is made that 20 per cent of the people living around Lake Geneva are infested and that 9 per cent of the inhabitants of Moscow harbor the parasite. The intermediate host is the fish. Man is infested by eating raw or improperly cooked fish containing the cysticercus stage of the parasite.

*Bothriocephalus* infestation is distinctly unusual in the United States. Cases are of more than passing interest on account of their rarity alone. Singer,<sup>2</sup> in reporting a case, was able to find only 30 cases reported in this country up to 1916. Since that time single cases have been reported by Rubenstone,<sup>3</sup> Kopelowitz,<sup>4</sup> McGoffin,<sup>5</sup> Levy and Wall,<sup>6</sup> Savitz,<sup>7</sup> and Wallace and Grant,<sup>8</sup> and 6 cases by Becker.<sup>9</sup> Of the 30 cases found by Singer reported before 1916, only 1 had originated in the United States. One of the cases reported by Becker and the case reported by Wallace and Grant were native born. It is evident that the fish in certain districts of this country must be infested. If so, it is only a matter of time before more cases will be reported as originating here.

Clinicians are interested in *bothriocephalus* infestation not because of its rarity, but by reason of the anemia which may occur in the infested individual. It is said that about 10 per cent of those harboring the parasite at some time develop an anemia. In a considerable percentage of cases the anemia cannot be distinguished clinically from true idiopathic pernicious anemia, thus differing from the secondary type of anemia occurring in other kinds of parasitic infection.

This then is one of the few conditions in which there is an anemia of known etiology which so closely simulates pernicious anemia. It has for this reason excited the interest of many research workers in the hope that the solution of the cause of the anemia in *bothriocephalus* infection might throw some light on the origin of pernicious anemia.

The cause of the primary type of anemia in this disease has been variously explained. It has been thought by some that certain lipoids of the worm might be the hemolytic agent. Attempts to reproduce the anemia with extracts of the normal worm have not

been successful. Schaumann and Tallquist<sup>10</sup> found however, that by feeding or injecting subcutaneously dogs with worms which had been subjected to tryptic digestion an anemia could be produced. In one dog the anemia was fatal, in the other the red-cell count was reduced one-half. They found also that similar extracts were hemolytic *in vitro* for blood of the dog.

Faust and Tallquist<sup>11</sup> noted that the worms recovered from cases having an anemia show as a rule a great loss of substance. There was sometimes almost a complete solution of the proglottides. They found that on an average there was a 60 per cent loss of dried substance per unit of length as compared with the normal worm. There was little change in the lipid content. The cause of the disintegration was not clear. They advanced the theory that through death of the parasite in the intestinal canal of the host hemolytic substances were absorbed and brought about the characteristic action on the blood and bone-marrow. The time and extent of the absorption would determine whether or not there is an anemia, the anemia developing only when there is a relative insufficiency of the bone marrow.

These observations of Faust and Tallquist seem to have received little recognition. Their theory is seldom mentioned in a discussion of the cause of bothriocephalus anemia. We have had the opportunity of studying a case of bothriocephalus infestation in which there is much to suggest that the onset of the anemia was due to the death of the worm. The case history is as follows:

**Case History.** F. A., a laborer, aged thirty-two years, admitted to the Henry Ford Hospital, March 23, 1921.

**Complaint.** Dizziness, pain in leg, weakness and difficulty of vision.

**Family History.** Unimportant.

**Personal History.** The patient had come to this country from Finland in 1914. He stated that he had had none of the usual childhood diseases. He had had three attacks of pneumonia. He gave a history of nycturia. He had passed segments of a tapeworm at intervals for the past three years. Otherwise he had been entirely well.

**Present Illness.** Five weeks before admission he began to have pain and swelling in the right knee and ankle. The pain was present only on motion. At the same time he noticed a small red papular eruption over both legs. Soon after a large purple area appeared on the inner surface of the left knee. He continued to work, but became progressively weaker. For a week he had had some dimness of vision and had been dizzy on exertion for two weeks. He complained of an indefinite pain in the epigastric region and had vomited once.

**Physical Examination.** The patient was evidently ill. There was a slight fever; the pulse was 96. There was no glandular

enlargement. Examination of the head, lungs, heart and abdomen showed no abnormality. The blood-pressure was 120/70.

Over the thighs, legs and to a less extent over the back, there were numerous petechiæ. There was a very large ecchymosis about the left knee and down the left leg. Purpuric spots were present on the uvula and hemorrhages were found in the retina.

The left knee was painful on passive motion. There was some tenderness on pressure at the medial margin of the left patella. No fluid could be demonstrated in the knee-joint. Both knees subsequently showed a yellowish green discoloration in the subcutaneous tissues. The appearance suggested a sanguineous effusion in the joint. The gums were spongy and hemorrhagic.

*Laboratory Findings.* Urine: Specific gravity 1012 to 1028, albumin and sugar negative, microscopical examination negative. Blood count: Red blood cells, 2,664,000; white blood cells, 4950; hemoglobin 50 per cent; differential count: neutrophiles, 69 per cent; eosinophiles 0; basophiles, 1 per cent; small mononuclears, 25 per cent; large mononuclears, 5 per cent. Wassermann negative. Blood culture negative. Examination of the stool revealed large numbers of the ova of bothriocephalus latus.

*Subsequent Course.* Two days after admission the red cell count had dropped to 2,000,000 and the hemoglobin to 40 per cent. As soon as ova were discovered in the stool, treatment was instituted. A specimen of bothriocephalus latus approximately 35 feet in length was passed. The ecchymosis and purpuric spots disappeared. The joint signs and symptoms cleared up. The anemia began to improve at once. Sixteen days after admission the red cell count was 3,673,000, and ova could no longer be found in the stool. The patient was discharged after a stay in the hospital of twenty-five days.

*Discussion.* The patient had resided in this country six years. He had come from Finland where infestation with bothriocephalus latus is exceedingly common. In all probability he had acquired the infection before coming to the United States. He had passed segments of a tapeworm at intervals for at least three years. There is every reason to believe that the worm had been in the intestinal tract for at least six years.

The patient had remained perfectly well however; until the sudden onset of the present illness. On recovering the worm its segments were found to be densely intertwined. A large part was glistening and gelatinous, and evidently undergoing disintegration. The rest of the worm looked perfectly normal. The parts of the worm were so intertwined that the decomposing parts could not be cast off until the dissolution was complete.

These findings are in accord with Faust and Tallquist's observation that the worms recovered from patients with an anemia, show a great loss of substance. The history and the findings suggest

that the onset of symptoms in this case was due to the death of the worm and the anemia, due to absorption of decomposition products.

**Summary.** A case of bothriocephalus latus infestation is reported. The patient had probably harbored the parasite for six years without showing any symptoms. There was an anemia of sudden onset which quickly disappeared after the worm was expelled. When recovered a large part of the worm was in a state of decomposition. These findings lend support to the idea expressed by Faust and Tallquist that the anemia of bothriocephalus infestation is due to the absorption of hemolytic substances from the dead worm.

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### CEREBROSPINAL FLUID PRESSURES: CONCERNING AN INITIAL FALL IN PRESSURE READINGS AND THE METHOD OF OBTAINING A STANDARD READING.<sup>1</sup>

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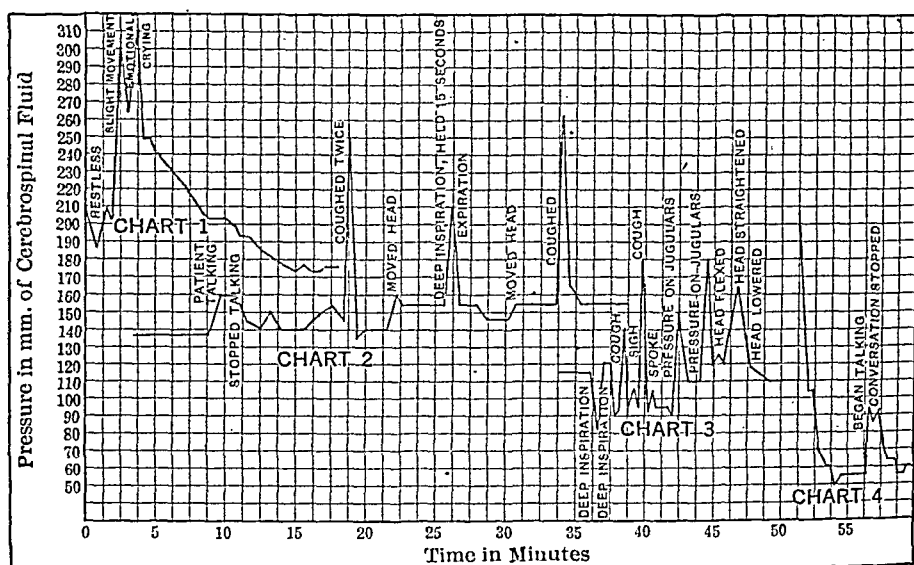
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THE reading of the cerebrospinal fluid pressure manometer taken shortly after a lumbar puncture has been performed does not represent the cerebrospinal fluid pressure that exists under conditions of rest and equilibrium. The reading immediately following the lumbar puncture may be 300 or 400 per cent or more in excess of the pressure that will be obtained at the end of five to ten minutes or thereabouts, and this latter pressure will often remain constant as long as the patient is quiet and does not move.

<sup>1</sup> This work was greatly assisted by a grant of funds from the United States Interdepartmental Social Hygiene Board.

The ordinary method of taking the cerebrospinal fluid pressure is to perform a lumbar puncture with the patient lying on his side on a level table. A manometer is then attached to the lumbar puncture needle and the reading made of this manometer. Either a mercury manometer or a standpipe recording the height to which the cerebrospinal fluid rises may be used. In either case the principle is quite the same and should represent the tension of the cerebrospinal fluid at that moment. In our experiments a standpipe manometer was used to record the fluid pressure. The point we wish to emphasize is that the tension of the spinal fluid measured in this manner varies under different conditions, and these variations may be of considerable amount.

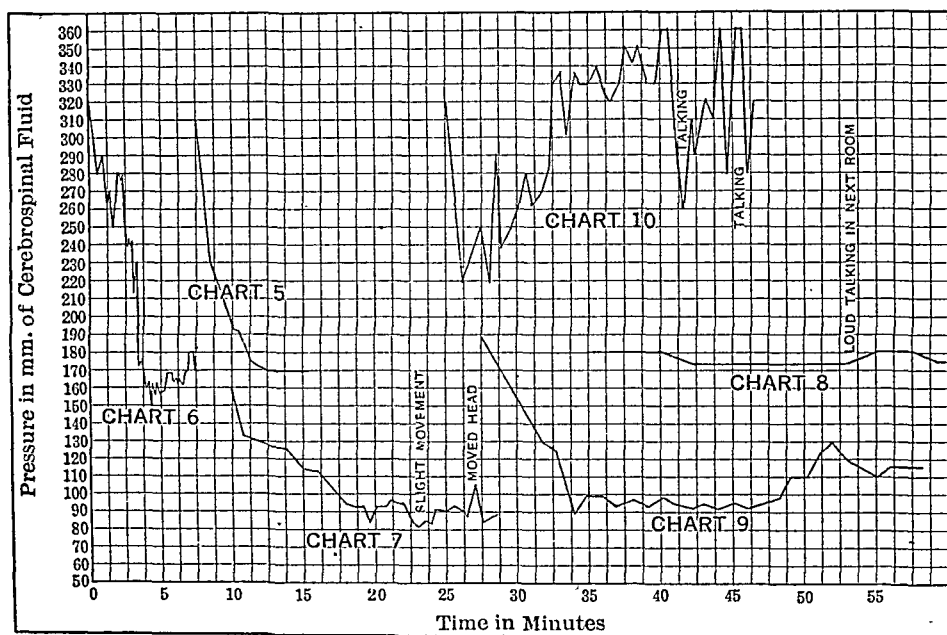


The first three charts (1, 2 and 3) indicate the effect of talking, coughing, movement of the head, pressure on the jugulars, forced respiration,<sup>2</sup> etc. All of these phenomena cause a considerable change in the reading of the spinal fluid manometer. The charts indicate that a change in pressure may occur. It is obvious, therefore, that one must guard against these variations in making a reading which is to represent the ordinary pressure of the cerebrospinal fluid. If the patient remains absolutely quiet and is under no great emotional strain, the reading in the manometer will reach a level at the end of five to ten minutes, which level will be maintained approximately as long as the patient is quiet.

<sup>2</sup> In Chart 2 it will be noted that a deep inspiration caused a rise in the pressure reading with a fall on expiration, whereas in Chart 3 a drop is recorded on inspiration and a rise on expiration, in other words a reverse is recorded on inspiration and expiration on the pressure reading in these 2 cases. Other observations have shown that in some individuals inspiration causes a rise, in others a fall. We are not clear as to the reason for this.

*This level, which is reached at the end of a period of minutes, may be considered as a standard for the cerebrospinal fluid pressure under the given conditions.*

In a vast majority of cases the reading obtained immediately after a lumbar puncture is much higher than that obtained at the end of some ten minutes. During the first portion of this ten minutes the drop is relatively great. At the end of the first three or four minutes the rate of drop becomes slower, and after seven to ten minutes a level is reached which is likely to be maintained thereafter if the patient is quiet. Although the initial drop is quite rapid, as shown in the charts, unless one is on the alert it may not be noted. The drop takes place in oscillations (see Chart 6), and the level will remain apparently stationary for several seconds,



which is about the length of time that one ordinarily observes the manometer. We wish strongly to emphasize this point, as in our own experience we were unaware of the falling level of fluid during a long period of cerebrospinal fluid pressure readings.

Out of a great many observations we present Charts 4 to 7 as illustrations of the drop that occurs. It will be noted that the preliminary drop may be very great and quite rapid, as shown in Chart 4, where the original reading was 200 mm., and at the end of three minutes the reading was 55 mm., which was maintained for two minutes until the patient began talking, when it rose to 90 mm., but again dropped to 55 mm., and then to 50 mm. after conversation ceased. Chart 5 shows a drop in the first thirty seconds from 310 mm. to 230 mm., and at the end of four minutes

a stable equilibrium was reached at 170 mm. Chart 6 shows a more irregular curve of the pressure readings. In this experiment readings were taken very frequently (*i. e.*, 13 to the minute). It shows that the drop takes place in oscillations with the level stationary for several seconds, as mentioned in the preceding paragraph. An initial reading of 320 mm. was followed by a drop to 250 mm. in the first ninety-second interval, which was succeeded by a rise to 280 mm., was unevenly sustained for nearly a minute, and then a fall to 150 mm. occurred. Chart 7 shows a case in which the drop was much slower and the fall from 160 mm. to 95 mm. or less did not occur until more than eight minutes had elapsed.

While an initial drop is the rule, it does not occur in every case, but, on the contrary, one finds at times that the original reading remains as the approximate level throughout a considerable period of observation. It is not possible, therefore, to assume that a certain percentage drop will occur in every case. In Chart 8 an observation is given in which during a period of twenty-five minutes there was hardly any change in the reading.

On the other hand, there may occasionally, although rarely, be a rise in the reading of a considerable degree. Thus, in the observation recorded in Chart 9 a drop from the original reading of 190 mm. to 100 mm. took place in the first seven or eight minutes, but at the end of eighteen minutes it again rose to 130 mm. Chart 10 represents a more marked increase. The patient was not accustomed to lumbar punctures and was quite restless, which may account for this rise. An original reading of 320 mm. was succeeded by a fall in the first minute to 220 mm., and then a rise began which is recorded in a sierra-like graph until at the end of fifteen minutes the fluid was forced out of the top of the manometer at 360 mm.

After having definitely established the observation that this drop occurs in the majority of cases, it became our interest to attempt to find an explanation of the phenomenon. The matter of local anesthetics seemed to have no appreciable effect whatsoever, as the same type of fall in pressure occurred both in the cases where the back was cocainized and in those in which it was not.

The position of the patient and the amount of emotional response seem to be important factors, of which the former takes the leading part. The usual method of performing a lumbar puncture in a horizontal position is to have the patient curl up to as great an extent as is possible, the legs flexed upon the abdomen and the head and shoulders fully flexed. Often an assistant will aid the patient in obtaining this position by placing one hand behind the knees and the other over the neck and shoulders and exerting pressure to flex the body. This position is shown in Fig. 1. It is under these conditions that the initial spinal fluid pressure reading will be found to reach its highest level and make its most marked

drop. This position puts the muscles of the patient under tension, it compresses the thorax and flexes the neck, making pressure upon the jugular vessels. All of these factors tend to cause a temporary



FIG. 1.—Patient flexed, knees drawn up and head bent as far forward as possible. Usual position when lumbar puncture is performed with patient in horizontal plane.

rise in the cerebrospinal fluid tension. This increase in pressure is temporary, and after a period of a few minutes "compensatory" changes occur which lead to an equilibrium.

The state of the patient's emotions with the resultant physiological effects also plays a part in the production of an increased

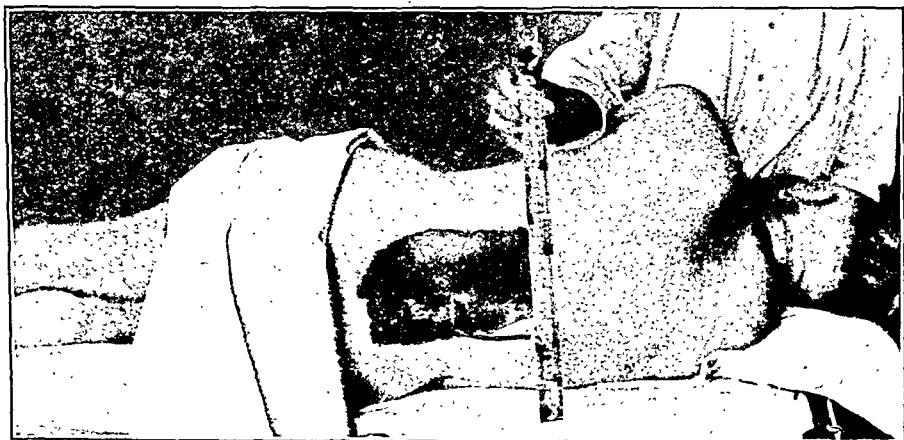


FIG. 2.—Lumbar puncture with patient extended. This position makes lumbar punctures more difficult than when patient is flexed.

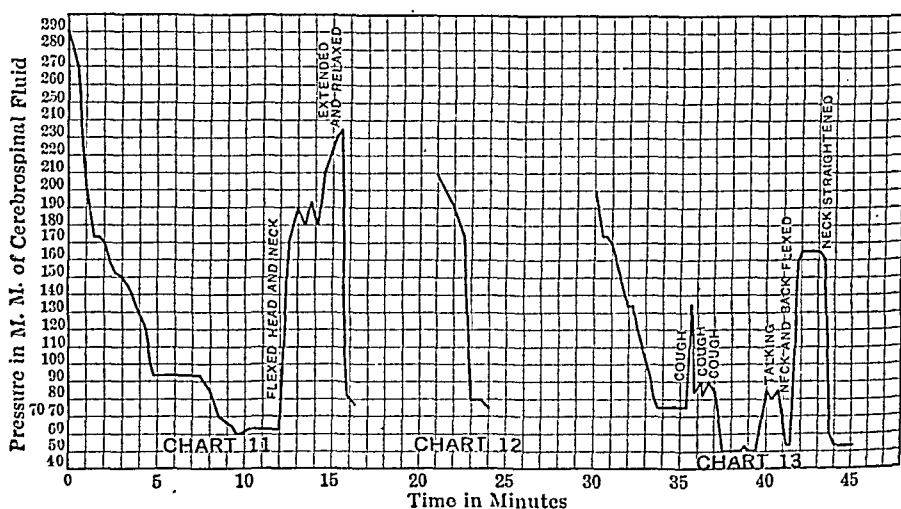
pressure, as is indicated in Chart 1, showing the effect of fear. That the emotional state may play a considerable part is also indicated by the fact that injections of pituitrin and adrenalin



will cause a rise in spinal fluid pressure. Emotional changes cause increase of endocrine secretion. However, the position of the patient is a more important factor.

If the puncture is performed with the patient extended, as shown in Fig. 2, then the original reading will be much lower than if the puncture is performed and the patient in the position of Fig. 1, and a secondary drop will not take place. That the position of the patient causes the changes just mentioned has been demonstrated by us a number of times, and we present several charts which graphically portray the results of the experiments.

Chart 11 shows the readings taken on a patient who was punctured when flexed. An initial spinal fluid pressure of 290 mm. of cerebrospinal fluid was obtained. A drop occurred so that at the end of ten minutes the spinal fluid pressure reading was 60 mm.



The patient's back was then voluntarily flexed at the physician's request and the pressure immediately began to rise, and at the end of thirty seconds it reached a level of 170 mm. and at the end of three and a quarter minutes had risen to 235 mm. The patient's back was then extended and he was told to relax, whereupon in less than one minute the pressure had again dropped to 75 mm.

Chart 12 shows the rapidity with which the fall occurred when the patient was extended and relaxed, after having been flexed for the puncture.

The effect of flexion of the head and neck is well illustrated in Chart 13, which also indicates the initial drop and the effect of coughing and talking. The puncture was performed with the patient in the flexed position. At the end of seven minutes the pressure in this case had dropped from the original 190 mm. of

cerebrospinal fluid to 50 mm., at which point it remained stationary for two minutes until the patient talked, when it rose to 85 mm., remaining at this level during the period that the patient talked and on cessation of the speaking it again fell to 55 mm. During this period the patient remained flexed, but he no longer held himself rigid. The head was then voluntarily flexed to a great extent by the patient, which caused an immediate rise of 110 mm., that is, from 55 mm. to 165 mm. This was maintained for nearly a minute, when the head was again straightened, when the pressure dropped rapidly to 50 mm., where it remained; thus in this case 50 mm. would seem to be the approximate pressure when at rest.

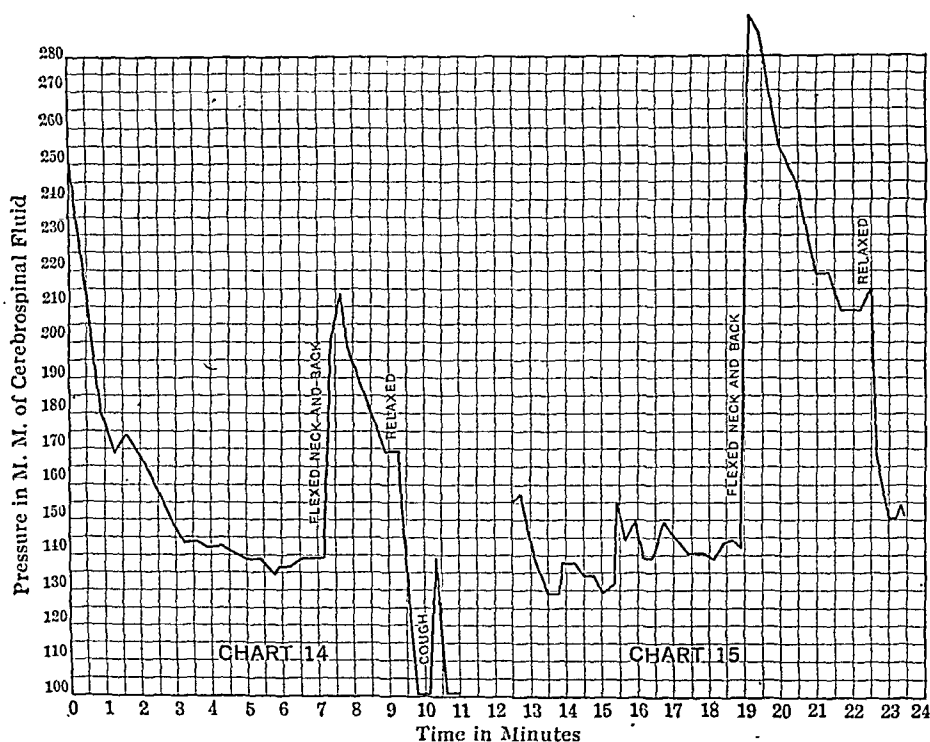


Chart 14 shows the initial drop, the rise on flexion, the secondary drop from this point which is apparently the result of the compensatory mechanism and then a further and more rapid drop that occurs upon relaxation. This experiment also shows that the relaxation and the extension of the body may cause the fall to go to a point lower than that which occurred during the preliminary drop due to compensatory mechanism alone. Even under these conditions it is not possible to be sure as to what is the real cerebrospinal fluid pressure, for after having obtained a reading that remains fairly constant for several minutes, slight changes either in position or degree of muscular tension or mental and

emotional responses may produce a further fall or a rise, as shown in Chart 9.

Chart 15 is a record of an observation in which puncture was performed on a patient accustomed to lumbar puncture. He was relatively extended and relaxed at the moment of puncture and relatively little variation in the pressure reading occurred in the subsequent six minutes. He then flexed his neck and back and the pressure reading rose in the course of a few seconds from 143 mm. to 290 mm., then slowly fell so that in about three minutes it registered 215 mm. He was then asked to relax and the reading promptly dropped to 150 mm.

It is not certain through what physiological channels these cerebrospinal fluid pressure variations, resulting from change in position, are due. The fluid pressure varies directly with the cerebral venous pressure and, to a lesser degree, with arterial tension. These are both increased in the flexed position with the muscles in contraction, while marked flexion of the neck causes jugular compression. Expectancy and fear cause increased arterial pressure. All these and probably other factors as well contribute to the increase in pressure noted.

What we have termed the "compensatory mechanism," whereby the marked rises and falls of pressure are compensated for and a stable equilibrium produced, is a matter of great theoretical interest. It is evident that through some process changes in the fluid tension are cared for and brought back to an equilibrium. After the needle has been inserted and nothing more seems to be happening, the patient will tend to relax, although he may not change his position perceptibly. This accounts for part of the preliminary drop. This matter will be taken up in a future paper. At present it suffices to call attention to the facts.

From these observations, we feel thoroughly convinced that readings of the cerebrospinal fluid pressure, in order to be of any value, must be done with exceedingly great care and must take into consideration the following conditions:

1. The patient should be relaxed both mentally and muscularly.
2. The observations must be made over a period of time of at least six or seven minutes.

3. The pressure must remain approximately constant for a period of two or three minutes before the reading can be accepted.

If these conditions are fulfilled a reading will be obtained which represents a reasonably stable pressure that exists in the patient when he is in the horizontal position and at rest. The reading obtained will depend somewhat upon whether the head is on a pillow or on the table at a level with the buttocks, whether the patient is leaning a little forward or backward, whether the needle is inserted in the median line of the dura or to the side. These factors, however, cause only a minimal variation and one that is

of no practical importance. We feel that the pressure readings obtained as outlined will serve as satisfactory standards for comparison.

These necessary conditions for approximate accuracy of spinal fluid pressure readings make it comparatively difficult to get a satisfactory reading on the average patient, unless he has been subjected to lumbar punctures previously and is fairly well trained. The average patient having his first puncture performed is fearful and tense, and he is unable to relax very completely, and is likely to fret and move if the procedure takes many minutes, as we have shown is necessary. Holding a manometer and observing it, one is apt to find five to ten minutes a long period, and unless one uses a timepiece to determine the time, he is very likely to overestimate the time that has elapsed.

When a puncture is performed, as is so often the case, upon a patient who is not coöperative, it is almost impossible to get a satisfactory pressure reading. The readings made upon patients with head trauma who are confused and resistive, or upon children who are struggling, are entirely without value because when struggling and being firmly held a reading of from 300 to 400 mm. or more may be obtained as a result of these factors, when the pressure under conditions of rest is probably not greater than 100 mm. Upon the basis of a reading of 300 or 400 mm., one might conclude that the patient was suffering from increased intracranial tension, which might not be true at all but rather a temporary rise as a result of a strained position.

Finally, we wish to call attention to the fact that in the ordinary course of human activity there are marked changes in the cerebrospinal fluid pressure. Strenuous muscular exertion must cause a temporary rise of a great extent as do various other factors. So in estimating the cerebrospinal fluid pressure one must attempt to use a standard. This standard will merely represent the pressure obtained under certain controlled conditions. The conditions that we consider absolutely requisite for obtaining workable standard of cerebrospinal fluid pressure have already been given.

**Summary.** When lumbar puncture is performed in the usual manner, with the patient lying upon his side and well flexed, the pressure recorded shortly after the needle is inserted is apt to be two, three or four times as great as that obtained after ten minutes. Usually a drop of pressure occurs, being quite rapid in the first two or three minutes, then less rapid for several minutes. Six to ten minutes after the puncture is performed, a stable equilibrium is reached and the pressure reading remains fairly constant from then on if the patient is quiet. This is not invariably true, but occurs in the majority of instances.

Several factors play a part in the production of the early high reading and subsequent fall. The most important are the position

of the patient and the amount of tension under which he holds himself. When rigidly flexed and fearful the pressure is always high. Relaxation and extension avoids this original fluid hypertension. If after the pressure has fallen the patient again makes himself rigid and flexes himself vigorously, the pressure will again rise and will fall once more. The rate of drop will be accelerated if the patient relaxes and extends himself. In order to have a standard for estimating cerebrospinal fluid pressure, it is necessary to observe the rules which are given above.

Readings taken upon patients who are fearful or struggling, as is often the case following head trauma, may be 300 or 400 per cent, or even more, in excess of the pressure existing during periods of rest and quiet.

### **STUDIES OF CEREBROSPINAL FLUID IN INFANTS AND YOUNG CHILDREN IN CONDITIONS OTHER THAN ACUTE MENINGITIS.**

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FROM October 1, 1915, to January 1, 1922, lumbar puncture was performed at the Babies' Hospital in about 800 different patients. The largest single group among this number was tuberculous meningitis; there was also a large number of cases of meningitis due to the meningococcus and a small number of other types of meningitis caused by pyogenic organisms. There were numerous cases of poliomyelitis, the majority of which occurred during the epidemic of 1916.

All the above mentioned cases have been excluded in the following study of the cerebrospinal fluid in 316 different patients. Blood-stained cerebrospinal fluids have also been excluded as well as all cases in which clinically there were any symptoms which might have been suggestive of poliomyelitis, even though paralysis was not demonstrable. The majority of the patients were under two years of age, a number were between two and three years, and a few between three and five. A brief survey of the physiology and anatomy of the cerebrospinal fluid may not be amiss:

The more modern interest in the cerebrospinal fluid dates from the important observations and masterly description of Magendie contained in his epochal monograph published in 1842.<sup>1</sup> Interest was further stimulated by Quincke's introduction of lumbar puncture in the living subject, which opened up a wide field for diagnostic possibilities in pathological conditions of the central nervous system.

Lying free in each ventricle are two highly convoluted vascular tufts, the choroid plexuses, the chief elaborators of cerebrospinal fluid. These project into the ventricles, carrying before them the lining epithelium. Mott<sup>2</sup> believes that one is justified in speaking of the plexus as the choroid gland.

The cerebrospinal fluid is contained in all the cavities of the ventricular system and in the subarachnoid space. It is probable that the fluids of these two spaces are not of common origin, although it has been proved that the major portion of the fluid is produced within the cavity of the ventricles.

Dandy<sup>3</sup> has proved conclusively that the fluid in the ventricles is produced by the choroid plexuses and not by the lining ependyma by the following experiment: He blocked the foramen of Monro on one side of a dog's brain, while on the other side he first removed the choroid plexus of the lateral ventricle, leaving the ependyma intact, and then blocked the foramen of Monro on that side. In the former case the ventricle became greatly distended with fluid, a condition of unilateral hydrocephalus, while in the latter it became shrunken and collapsed, and contained no fluid, although still lined by ependyma. Some portion of the cerebrospinal fluid is evidently extraventricular in origin and not simply due to a ventricular overflow through the openings in the roof of the fourth ventricle. Dandy and Blackfan<sup>3</sup> observed in a case of internal hydrocephalus with complete obstruction to the ventricular overflow that although only 5 cc of fluid could be withdrawn by lumbar puncture, shortly afterward a similar quantity could be withdrawn, which was obviously of extraventricular origin. Cushing and Goetsch<sup>5</sup> have endeavored to prove that there is an additional source of a small amount of fluid from the secretion of the posterior lobe of the pituitary gland, which is poured into the cerebrospinal fluid.

**Absorption of the Fluid.** All are familiar with the fact that cerebrospinal fluid is constantly being secreted in large quantities.<sup>6</sup> In fracture of the base of the skull, as well as in cases of cerebrospinal rhinorrhea, a large quantity of fluid may discharge in the course of twenty-four hours, although it is not clear whether this corresponds with the amount of fluid normally secreted during the same period.

Leonard Hill<sup>7</sup> has ably demonstrated that the major portion of the fluid passes into the blood. He noted that when methylene blue solution was injected into the cerebrospinal spaces the dye appeared in the bladder and stomach in from ten to twenty minutes.

The problem of how the cerebrospinal fluid finds its way to the cerebral circulation has been solved by Weed<sup>8</sup> by the following experiment: he showed that fluid containing granules of Prussian blue when injected into the subarachnoid space under pressure only slightly above that of the cerebrospinal fluid could be traced into villous-like processes, which project into the lumen of the sinus and eventually within the lateral walls of the sinus itself.

There is, in addition, an absorption of the fluid by way of the lymphatics (Boyd<sup>9</sup>), to which the fluid gains entrance by way of the perineural space which surrounds the nerves. When ferrocyanide solution is injected into the subarachnoid space the lymphatics of the neck have been found to be deeply stained. In all the spinal nerves, absorption from the perineural spaces into the lymphatics of the anterior and posterior nerve roots can be demonstrated by the ferrocyanide replacement method.

"It does, however, seem established, on definite and firm grounds, that the cerebrospinal fluid is largely produced within the cerebral ventricles by specially differentiated structures, the choroid plexuses. After traversing the ventricles, this fluid passes from the fourth ventricle into the subarachnoid spaces; these are channels adapted for fluid passage and permit the distribution of the fluid everywhere about the central nervous system. From these spaces the fluid returns to the blood-vascular system, the mode of absorption being a process largely of filtration and diffusion through arachnoid villi into the dural sinuses." (Weed.<sup>10</sup>)

In all the examinations of cerebrospinal fluid included in this study, the cell counts were made in a counting chamber and the globulin test was done according to the method of Noguchi. For the last three years, Benedict's solution has been used to determine the presence of a reducing substance, prior to that Fehling's solution was used. In only a limited number of the cases was the pressure of the cerebrospinal fluid determined by the manometer, in the balance of the cases it was entirely a question of personal observation.

It is generally agreed that the cerebrospinal fluid of normal infants and children is clear and colorless, slightly alkaline in reaction, with a specific gravity of approximately 1002. The pressure of the fluid when the child is in the recumbent position varies between 5 and 10 mm. of mercury. There is nearly always a positive reaction for a reducing substance. Globulin does not exist in demonstrable quantities in the normal cerebrospinal fluid, and when a positive globulin reaction is present the fluid is pathological. Lymphocytes are normally the only cells present in cerebrospinal fluid. In adults up to 8 per c.mm. may be considered normal. In children they are apparently somewhat more numerous, and as many as 20 per c.mm. may be found in a normal child. None of the specimens of cerebrospinal fluid submitted in this study were examined spectroscopically.

**Normal Children.** For comparison with the data furnished by lumbar puncture in the various groups of patients with different diseases the findings in 5 normal children are presented. The cerebrospinal fluid in all the cases was clear and colorless, and the average cell count was 4 per c.mm., with a count of 8 cells as the highest. In the 4 cases in which a test for a reducing substance was

done it was positive in all. The globulin test, which was done in all cases, was positive in none.

These findings in my experience represent a normal average for infants and children. The test for reducing substance is regularly positive, and the test for globulin should be negative.

For the purpose of study and comparison with the findings of others, the cases have been classified according to clinical diagnosis. Except in the cases of congenital syphilis, lumbar puncture was generally done in all these cases because of such suspicious symptoms as convulsions, rigidity of neck and back, bulging of fontanelle, projectile vomiting, extreme irritability, changes in pulse or respiration, disturbance of the sensorium, etc.

**Respiratory Cases.** There were 67 cases in which the primary diagnosis was some form of respiratory condition other than pulmonary tuberculosis. Thirty-nine of the patients were under one year of age; most of these were cases of bronchopneumonia. There were a few cases of lobar pneumonia and a lesser number of such conditions as pleurisy, bronchitis, influenza, etc. Some of the cases were complicated by other conditions not involving the central nervous system. Of the 67 cases 21 were autopsied.

Of the entire group of respiratory cases convulsions had been noted in 15. Of the 67 cases the cerebrospinal fluid was clear and colorless in 66. In 28 cases it had been noted on the chart that it was withdrawn under increased pressure. The amounts withdrawn varied between a few cc and 35 cc. In 11 cases, 20 or more cc was withdrawn, and in 24 cases, 15 cc or more was withdrawn. The average number of cells was 11.0 per c.mm. A differential count was made in only 44 of the specimens obtained, and in nearly all of these the majority of the cells found were lymphocytes. Only 41 of the specimens of cerebrospinal fluid were tested for a reducing substance, and in 37, or 90 per cent, the test was positive. The globulin test was made in 43 of the specimens and was only positive in 5 instances, or 11 per cent. In 9 cases a routine culture of the fluid was made and in each instance it was negative. Five of the cases in this group had findings sufficiently unusual to merit further study. Of these 5 cases all had a cell count of 30 or more cells and 4 numbered more than 60 cells per c.mm.

No. 18,441, aged five months, had a generalized eczema on admission. A clear cerebrospinal fluid was withdrawn containing 90 cells, all lymphocytes, with a positive test for globulin. The infant died of bronchopneumonia, and in addition a parenchymatous degeneration of the kidneys was found at autopsy.

No. 17,513, aged fourteen months, was admitted because of cough, restlessness, and high fever. Thirty-five cc of clear fluid was withdrawn under increased pressure, in which the cell count showed 70 cells per c.mm., all lymphocytes. The child died of acute bronchopneumonia, which was noted at autopsy in addition to a fatty liver.



No. 13,561, aged seven weeks, admitted because of convulsions. The clinical diagnosis was acute bronchopneumonia; the child was discharged cured of the condition for which he was admitted. Fifteen cc of clear fluid was withdrawn under pressure with 60 cells, 99 per cent of which were lymphocytes. A reducing substance was present, but the globulin test showed no increased amount.

No. 13,084, aged six months, was a somewhat similar case; admitted on account of cough, fever and drowsiness. The leukocyte count was 31,000. The cerebrospinal fluid was clear, under increased pressure, with 62 cells per c.mm., all lymphocytes. The globulin test was positive; the test for a reducing substance was negative. The clinical diagnosis was bronchopneumonia complicated by otitis media. The infant was discharged cured of the condition for which he was admitted.

No. 11,745, was a five-year-old boy who had a lobar pneumonia with an abrupt onset; vomiting and convulsions. The cerebrospinal fluid was clear and not under increased pressure. There were 30 cells per cm., 90 per cent of which were lymphocytes. The globulin test was negative. The boy made an uneventful recovery.

Lumbar puncture was done in 3 cases of pneumonia with positive blood cultures without symptoms of meningitis. The infecting organism in 2 of these was the pneumococcus, and in the third the streptococcus. In 1 case an autopsy was done. The cerebrospinal fluid was clear and colorless in the 3 cases, and the total cells per c.mm. numbered 3, 2 and 5 cells respectively. The test for a reducing substance was positive in all, and the test for globulin was negative in each case. The above findings, together with data noted elsewhere of septicemia caused by other organisms, are interesting, as they may be viewed as possible evidence of the protective mechanism in infants afforded by the choroid plexus in delaying a blood-stream infection from invading the central nervous system.

The analysis of these findings shows that in acute respiratory infections the great majority of cases has a normal cerebrospinal fluid, while a small minority (5 of 66) shows a fluid with an increased cell count, having in a few instances an increased globulin content. The highest cell count in this group was 90 per c.mm., and practically all were lymphocytes. From the findings in the first 5 cases the diagnosis of serous meningitis might well be justified.

In 15 of the cases convulsions were present. It will be noted here as well as elsewhere in this study that in only a few of the cases was pleocytosis associated with the presence of convulsions.

**Intestinal Cases.** The following group includes the cerebrospinal fluid findings of 50 cases in which the primary diagnosis was some type of intestinal disturbance. The diseases included under this heading were: acute gastro-enteritis, acute enteritis and ileocolitis, acute intestinal indigestion and intoxication, bacillary dysentery, etc. The diagnosis was made either on discharge of the patient

from the hospital, the result of a summation of the clinical symptoms, or at autopsy, which was done in 14 of the cases. Thirty of the patients were under one year of age, and the oldest child was aged four years. The majority of the patients in this group were admitted on account of frequent stools, vomiting, loss of weight, etc. A number of complications were noted, chiefly respiratory, and acute otitis media.

Every cerebrospinal fluid examined in this group was clear and colorless. In 18 patients it was under increased pressure. Among 35 in which a test for a reducing substance was made it was found positive (normal) in 31, or 88.5 per cent. In 34 cases in which the globulin test was done it was found positive (abnormal) in only 3, or 8.8 per cent. The average cell count for 49 cases was 7.7 cells per c.mm. In nearly every instance the only cells found were lymphocytes. In 7 cases the fluid was cultured for organisms with negative results. Only 4 cerebrospinal fluids were examined in which 20 or more cells were found.

The following 4 cases are of especial interest because of the relatively high cell counts:

No. 16,521, aged twenty-seven months, admitted on account of vomiting, irritability, and anorexia, had a clear cerebrospinal fluid not under increased pressure, containing 24 cells per c.mm.; 3 of the cells were polymorphonuclear leukocytes and 21 lymphocytes. The globulin test was positive and a reducing substance was present. The child was discharged improved after the nervous symptoms had disappeared, with a diagnosis of chronic intestinal indigestion.

No. 18,564, aged four weeks, admitted on account of frequent green stools. Fifteen cc of clear fluid was withdrawn which was not under increased pressure, with 21 cells, 95 per cent of which were lymphocytes. The culture was negative and the globulin test was positive. The infant was discharged cured, with a diagnosis of acute intestinal indigestion.

No. 14,052, aged four and a half months, admitted on account of fever, cough, and labored respiration. The child was highly irritable and definite rigidity of the neck was present. The clear cerebrospinal fluid was not under increased pressure, and contained 20 cells per cm., all of which were lymphocytes. The globulin test was negative. There were no organisms present. A reducing substance was present. At autopsy acute catarrhal colitis, fatty infiltration of the liver, atelectasis, and emphysema of the lungs were found. An examination of the brain was not permitted.

No. 19,741, aged sixteen months, was admitted on account of convulsions, vomiting, drowsiness, and diarrhea. Five cc of clear cerebrospinal fluid was withdrawn which was not under increased pressure. There were 20 cells present, of which 18 were lymphocytes. No organisms were discovered. The clinical diagnosis was acute intestinal intoxication. The child was discharged cured.

In acute and chronic intestinal conditions in infancy and early childhood the great majority of cases had a normal cerebrospinal fluid, while a minority (4 of 50) showed a fluid with a slightly increased cell count, 2 having increased globulin. The highest cell count in this group was 24 per c.mm.; nearly all were lymphocytes.

The severity of the disease evidently bore no relation to the cerebrospinal fluid findings, as the analysis of the 14 cases which were autopsied indicate. In these 14 cases the highest cell count was 20 cells per cm.m., and in none was the globulin reported positive.

**Tetany.** Lumbar puncture was done in 31 cases in which the diagnosis was tetany. Twenty-six of these patients were admitted on account of convulsions, 25 were under one year of age. All but 3 were discharged from the hospital improved or unimproved of the condition for which they were admitted. In the 3 who died, autopsies were not obtainable. On the discharge records of 11 some complication was noted, the most frequent of which was rickets.

The cerebrospinal fluid in all the cases was clear and colorless, and in 15 instances was withdrawn under increased pressure in amounts which varied between 5 and 25 cc. The average number of cells per c.mm. was 7.4; 5 of the fluids had 15 or more cells. In all but a few of the specimens of fluid the only cells were lymphocytes. In 20 cases in which a test for globulin was done it was found positive in 1 case and slightly positive in another. In 6 cases in which the cerebrospinal fluid was cultured all were reported negative.

Of especial interest are the following cases because of their atypical cerebrospinal fluid findings:

No. 19,238, aged three months, admitted on account of vomiting, convulsions, and rigidity of neck. The infant had an exceedingly well-marked Chvostek reaction. Five cc of clear fluid was withdrawn with 25 cells per c.mm., all of which were lymphocytes. The Pirquet test was positive. The child was discharged from the hospital improved of the condition for which he was admitted, and was not seen subsequently.

No. 19,434, aged twenty months, was admitted on account of fever, irritability, and convulsions. Five cc of clear fluid was withdrawn not under increased pressure, with 30 cells per cmm. The Chvostek reaction was marked. The child was discharged improved with a diagnosis of tetany complicated by nasopharyngitis.

An interesting observation regarding the patients with tetany was the low average cell count in a group of cases in which all but 5 had convulsions. This is fairly conclusive evidence that even repeated convulsions bear no relation to the number of cells in the cerebrospinal fluid of infants and very young children.

In all the cases of tetany the cerebrospinal fluid was essentially normal; in a small number only (5 of 31) showed a fluid with a slightly increased cell count.

**Pyelitis.** Lumbar puncture was done in 6 infants acutely ill with pyuria, all of whom were under one year of age. Four of these were discharged cured from the hospital, with a diagnosis of pyelitis. Two died and came to autopsy. In 1 pyelonephritis, bronchopneumonia, and follicular colitis were found, and in the other parenchymatous degeneration of the kidneys, fatty liver, and a general visceral congestion. Two of these infants were admitted because of convulsions, the others because of drowsiness, vomiting, fever, etc. The cerebrospinal fluid was clear and colorless in every patient, and in no instance was it under increased pressure. The average count for the 6 cases was 12 cells per c. mm., and in only 1 case were there as many as 20 cells. This was noted in an infant; aged eleven months, who died of pyelonephritis with uremia. There was a reducing substance present in 5 of the specimens of cerebrospinal fluid, of which only that number were tested. The globulin test was negative in all of the 6 cases.

The cerebrospinal fluid was uniformly normal in 6 infants acutely ill with pyuria. The cerebrospinal fluid was clear and colorless with a reducing substance present, no increase in globulin, and having an increased number of cells in but 1 case.

**Neuropathic Children.** Four children in whom lumbar puncture was done were discharged with the notation that they were "neuropathic children" in whom no disease was established. The youngest of the 4 was aged twenty-one months, and the oldest three and a half years. They were admitted on account of symptoms suggesting tuberculous meningitis. Two were discharged cured and 2 improved of the symptoms for which they were admitted. The cerebrospinal fluid in the 4 cases was clear and colorless and in only 1 instance was it under increased pressure. The cell counts were 2, 10, 15, and 30 cells respectively. Two of the specimens of cerebrospinal fluid had negative cultures which included the case showing 30 cells per c.mm., and in the others cultures were not made. The globulin was negative in all 4 cases, and the test for a reducing substance was positive in every case. That is, all 4 had normal cerebrospinal fluids, 1 of which showed an increased number of cells.

**Otitis Media.** Lumbar puncture was done in 8 cases in which the only disease noted was acute otitis media. In 4 of the cases the disease was bilateral. The cerebrospinal fluid findings are presented in these cases as evidence against the belief held by some clinicians that there may be an increased cell count in acute middle ear infections. Otitis media is a frequent complication among patients tabulated in the entire study. It might be questioned whether the complicating middle ear infection might not have been the cause of some of the unusual cell counts in certain of the cases rather than the primary condition of pneumonia, etc. The normal cerebrospinal fluids which were found when the otitis was the only disease present proves rather conclusively that otitis in itself exerts no change in

the cerebrospinal fluid. Nor is there any reason why this should not be so. The average age of the 8 cases was ten months. In every instance the fluid was clear and colorless with the pressure increased in 3. The average number of cells per c.mm. was 5.6 and the highest count only 10 cells. Among 4 specimens tested for a reducing substance, 3 were positive. The globulin test was positive only once in the 8 cases.

The cerebrospinal fluid of 8 cases of acute otitis media was essentially normal in 7 cases with no increase of cells in any of the cases. In 1 case with a clear cerebrospinal fluid containing 10 polymorphonuclear leukocytes per c.mm., globulin was present in sufficient amount to cause a reaction.

**Cerebral Thrombosis.** Lumbar punctures were done in 5 cases of cerebral thrombosis proved at autopsy, 3 of which were due to sepsis and 2 to marasmus. The patients were aged fourteen months, sixteen months, nineteen days, seven and a half months, and seventeen months, respectively. In 2 cases the cerebrospinal fluid was cloudy yellow in color; the balance were clear and colorless.

No. 16,265, a septic case of thrombosis, was admitted because of vomiting and twitching of the right side of the body. Twenty cc of cerebrospinal fluid under normal pressure was removed. It contained 32 cells, of which 60 per cent were polymorphonuclear leukocytes and 40 per cent were lymphocytes. No film was present and no organisms were discovered. A reducing substance was present. At autopsy a thrombosis of the lateral and longitudinal sinus was found in addition to mastoiditis and cerebral hemorrhage.

No. 16,060, a case of marantic thrombosis, aged sixteen months, was admitted because of stupor. The leukocyte count was 40,000. Seventy-five cc of clear cerebrospinal fluid was withdrawn under greatly increased pressure. Only 5 cells were found, 3 of which were lymphocytes. The globulin test was negative; the test for a reducing substance was positive. There were no organisms found. At autopsy, cerebral thrombosis and hemorrhage were present, in addition to otitis media and congenital cardiac anomaly.

No. 18,580, a case of marantic thrombosis, aged nineteen days, admitted on account of dyspnea and rigidity of neck. Ten cc of yellow cloudy fluid under normal pressure was withdrawn which contained 46 cells, of which 25 per cent were lymphocytes and 75 per cent polymorphonuclears. The test for globulin was positive. At autopsy multiple cerebral thrombi were found as well as multiple cerebral hemorrhages. The yellow color is thus explained.

No. 16,873, a case of septic thrombosis, aged seven and a half months, was admitted because of enlargement of the head, stupor, and vomiting. The fontanelle was tense and the knee jerks exaggerated. The cerebrospinal fluid was clear and under normal pressure; 2 cells were found both of which were lymphocytes. A reducing substance was present, the globulin test was negative. Cerebral

thrombosis and internal hydrocephalus were present at autopsy, in addition to osteomyelitis of the malar bone. The hydrocephalus is difficult to explain with 2 cells only per c.mm., and a negative globulin test.

No. 20,690, aged twenty-nine and a half months. The cerebral spinal fluid was yellow tinged, faintly turbid, with a normal pressure, 8 lymphocytes, and 530 crenated red blood cells were found. The globulin test was positive, a reducing substance was present, and the culture negative.

At autopsy, thrombosis of cerebral sinuses and veins, cerebral softening, acute leptomeningitis, and hypostatic pulmonary congestion were present.

In only 1 of the 5 cases was the cerebrospinal fluid under increased pressure. The average cell count for the 5 cases was 18 cells per c.mm. In 2 of the cases the polymorphonuclear leukocytes predominated. The reaction for a reducing substance was positive in 4 cases in which the test was done, and the globulin test was positive in 2 of 4 tests. It would appear from the findings in the limited number of cases here presented that there is nothing pathognomonic in the cerebrospinal fluid of cerebral thrombosis. It is significant that 2 of the cases showed a yellow colored fluid, apparently the result of a hemorrhage following thrombosis.

**Congenital Syphilis.** Lumbar puncture was done in 20 cases of congenital syphilis. In 8 the diagnosis was proved at autopsy and in the others either by florid clinical manifestations or by the Wassermann test, or both. The average age of the patients in this group was ten and six-tenths months; 12 were less than six months of age. In former years lumbar puncture was done in congenital syphilitic cases only when an invasion of the meninges was suspected. More recently it has been done somewhat routinely in such cases.

In every case but 2 the cerebrospinal fluid was clear and colorless, and in only 6 instances was increased pressure noted. From 5 to 50 cc of fluid was withdrawn. Excluding the 3 cases proved at autopsy to be syphilitic meningitis, the average cell count for the remaining 17 cases was 15.5 per c.mm. Lymphocytes predominated in all the differential counts of the cells and in most instances no polymorphonuclears were found. A test for a reducing substance was done in only 11 cases, and in 8 was positive.

The globulin test which was done in all the cases was positive in 9, faintly positive in 1, and in the remaining 10 negative. Although the average cell count in the cases of congenital syphilis runs slightly higher than the number generally considered normal, there is great variability in the different cases. The specimens of fluid with the highest counts (with the exception of one of the cases with cerebral lues) occurred in infants in the first few months of life. Especially interesting are the low cell counts (5-7-5) in 3 cases with a positive Wassermann reaction of the cerebrospinal

fluid, which suggests that congenital syphilis may involve the central nervous system without increase in the number of cells in the cerebrospinal fluid.

The intensity of the demonstrable syphilitic manifestations apparently may have no relation to the number of cells in the cerebrospinal fluid, as case No. 17,781 illustrates. This was a three weeks old infant who had, in addition to the common syphilitic manifestations, general anasarca. Five cc of clear cerebrospinal fluid was withdrawn under normal pressure. Only 3 cells were found, and the globulin test was negative. The autopsy diagnosis were congenital syphilis with acute bronchopneumonia, chronic interstitial splenitis, acute splenic tumor, and degeneration of the kidneys. An examination of the head was not permitted.

No. 20,219 is an example of a child with severe manifestations of infection and a high cell count of the spinal fluid. This occurred in a nine weeks old infant admitted on account of general anasarca in addition to cutaneous syphilitic manifestations. The cerebrospinal fluid was clear and colorless and contained 44 cells, all of which were lymphocytes. There was a reducing substance present, and the globulin test was negative. The autopsy diagnosis was congenital syphilis with chronic interstitial splenitis, chronic perisplenitis, chronic interstitial hepatitis, acute diffuse nephritis, and general anasarca. Permission to examine the head was not obtainable.

The cerebrospinal fluid findings in the 3 following cases of syphilitic meningitis (proved at autopsy) are important:

No. 11,897, aged one year, with a luetic history on the paternal side and a mother who gave a history of 2 stillbirths and 2 infants who died directly after birth; all premature. The child was admitted because of vomiting, increasing drowsiness, and retraction of the head. The infant died four days after admission. Fifteen cc of slightly turbid cerebrospinal fluid was withdrawn under moderately increased pressure, with 650 cells per c.mm., 66 per cent of which were lymphocytes. The globulin was moderately increased. The cerebrospinal fluid of 3 lumbar punctures showed little variation. The cultures were negative; no tubercle bacilli were present. Autopsy showed congestion of the meninges and edema of the pia. Small, thickened grayish-white patches were noted over the pia mater in the sulci of the parietal and temporal lobes. There was considerable softening of the brain. Hemorrhages and minute thrombi in the gray matter were found. A moderate hydrocephalus was present.

No. 19,042, aged four months, was admitted because of drowsiness and irritability of two days' duration. The parents were both luetic. The infant died two days after admission. Eight cc of semi-turbid cerebrospinal fluid was withdrawn by lumbar puncture under increased pressure, with 810 cells per c.mm., 90 per cent of which

were lymphocytes and the balance polymorphonuclears. The globulin test was positive. No organisms were found. At autopsy it was found that the vessels of the pia were uniformly congested over all the surfaces of the cerebrum and cerebellum. The pia was slightly cloudy and thickened, especially over the interpeduncular space at the base.

No. 12,092, aged nine weeks, admitted because of convulsions of twelve days' duration and cyanotic attacks dating from birth. The child died two weeks after admission to the hospital. Eight cc of clear and colorless fluid was withdrawn by lumbar puncture under normal pressure. The test for globulin was negative with both the Noguchi and the ammonium sulphate methods; the test for a reducing substance was negative; 8 cells per c.mm. were found, of which 99 per cent were lymphocytes. No tubercle bacilli were present. The autopsy showed congestion of the pia over both sides of the cerebrum and a turbid pia over the base of the brain. In addition to the syphilitic meningitis, perisplenitis, parenchymatous degeneration of kidneys, and asymmetrical microgyria were noted.

The cerebrospinal fluid in congenital syphilis is clear and colorless (excepting in certain cases of syphilitic meningitis), and usually under normal pressure. The cytology is a variable factor. There is evidence in this series of cases to demonstrate that there may be involvement of the central nervous system without pleocytosis. The intensity of the clinical manifestations is apparently not a criterion to the cytology.

**Brain Tumor.** Twenty-one patients on whom lumbar puncture were done were diagnosed clinically as brain tumor. In 8 cases the diagnosis was proved at autopsy; in another it was proved by the subsequent course as observed in another hospital. The average age of the children in this group was approximately three years. Most of these children were admitted on account of such symptoms as vomiting, headache, disturbance of vision, abnormal gait, and convulsions.

In at least 11 of the patients the tumor was so far advanced that the diagnosis was made on admission to the hospital. In 6 of the cases which came to autopsy the tumor was found to be a glioma, in the other 2 the type was not recorded. In 2 of the cases the clinical diagnosis was tuberculoma, and in the balance of the patients it was stated to be cerebral or cerebellar tumor. The cerebrospinal fluid was clear and colorless in all but 2 of the cases; in 1 of these it was yellow and in the other straw colored. In only 13 of the cases was the fluid withdrawn under increased pressure.

Amounts varying between 2 and 3 cc were withdrawn by lumbar puncture. The average cell count was 52.2 cells per c.mm. A differential count was made in only 9 of the cases, and in 7 of these there was a great preponderance of lymphocytes. Both of the counts with a preponderance of polymorphonuclears were in cases which



came to autopsy. One was a cerebral gliosarcoma with hydrocephalus, and the other a neoplasm of the cerebrum with a chronic pachymeningitis. Although there was a high average cell count for the group of brain tumor cases, caused by a few relatively high counts, the general average for the balance was low, as there were 13 counts which were not higher than 15 cells per c.mm. Among tests made for a reducing substance in 16 cases 12 were positive. Of 16 globulin tests only 6 were positive. Of 7 Wassermann tests all were negative.

Two cases have been selected, both proved by autopsy, which illustrate the variable fluid findings both as to cell count, globulin, and reducing substances.

No. 13,855, aged ten months, admitted on account of vomiting of three weeks' duration. The fontanelle was tense and bulging, the knee jerks were exaggerated; the infant was quite drowsy. The leukocyte count was 13,000 and the temperature normal. Twenty cc of clear fluid was withdrawn under pressure, which contained 90 cells per c.mm., of which 91 per cent were lymphocytes and 9 per cent polymorphonuclear leukocytes. There was no reducing substance present, the Wassermann of the spinal fluid was negative, and the globulin test positive. At autopsy a cerebellar glioma was found which had caused internal hydrocephalus.

No. 20,035, aged thirteen months, was admitted on account of progressive loss of weight and vomiting, which began five months prior to admission. Fifteen cc of clear fluid, not under increased pressure, was withdrawn by lumbar puncture. The fluid contained only 13 cells per c.mm., of which 12 were lymphocytes and 1 a polymorphonuclear leukocyte. There was no film. The test for a reducing substance was positive, and the globulin negative. At autopsy a subpial cerebellar tumor was found, bronchopneumonia, acute mediastinitis, and retropharyngeal abscess.

All the cases of brain tumor but 2 had cerebrospinal fluid that was clear and colorless, and in only 13 of the 21 cases was the fluid withdrawn under increased pressure. In 11 of the 21 cases the cell count was not more than 10 per c.mm. The average for 20 cases was 52.2 per c.mm. and the highest was 240. Among 16 tested for a reducing substance all but 4 were positive. In 15 tested for globulin only 6 were positive. One is impressed by the fact that the cerebrospinal fluid in the cases of cerebral neoplasm presented in this study shows nothing pathognomonic.

**Tuberculosis.** Lumbar puncture was done in 7 cases of tuberculosis without symptoms of tuberculous meningitis, 6 of which were cases of acute general miliary tuberculosis (3 proved at autopsy) and 1 of pulmonary tuberculosis with a complicating corneal ulcer. All of the patients were under one year of age but 1, who was aged four years. The specimens of cerebrospinal fluid were clear and colorless in every case, and the average cell count for 6 cases was 12.5

cells per c.mm. Of 5 cerebrospinal fluids tested for a reducing substance all were positive. Differential counts of the cells were done in only 4 cases; 3 of these showed a great preponderance of polymorphonuclear leukocytes, which might possibly be explained as a reaction to beginning invasion of the meninges. The diagnosis of tuberculous meningitis is made at the Babies' Hospital only when tubercle bacilli are found in the spinal fluid.

Case 17,718 is of interest, as it demonstrates that an extensive pulmonary and miliary tuberculosis may exist without an invasion of the meninges by the tubercle bacilli. The patient was twelve months of age, admitted on account of cough, fever, and somnolence. The right ear was discharging and, as a right facial paralysis was present, this was probably a tuberculous otitis. Ten cc of clear cerebrospinal fluid under normal pressure was withdrawn with 12 cells per c.mm., 80 per cent of which were lymphocytes. The globulin test was positive and a reducing substance was present. Three lumbar punctures were done in an effort to find tubercle bacilli, but none were demonstrable. At autopsy general miliary tuberculosis was found in addition to tuberculosis of the lungs. Permission to open the head was not obtainable. The presence of 90 per cent of polymorphonuclears in Case 11,925 is difficult to explain. The patient was ten months of age and admitted on account of rigidity of the neck and back. Fifteen cc of clear cerebrospinal fluid was withdrawn under pressure with 32 cells per c.mm., 90 per cent of which were polymorphonuclear leukocytes. No tubercle bacilli were found; the test for a reducing substance and the globulin test were positive. At autopsy miliary tuberculosis of the lungs, spleen, liver and lymph nodes was found. Permission to open the head was not obtainable.

The analysis of the few cases of general miliary tuberculosis show that the cerebrospinal fluid is essentially normal, always clear and colorless with a reducing substance always present. Once only in 6 cases was an increased cell count noted, and in 2 of 3 cases autopsied the test for globulin was positive.

**Status Lymphaticus.** Lumbar puncture was done in 4 cases which at autopsy were found to be status lymphaticus. The patients were aged twenty-eight months, two and a half months, three months, and nine weeks, respectively. Two were admitted because of convulsions and the others for symptoms suggestive of meningitis. In the 4 cases the cerebrospinal fluid was clear and colorless, and in 3 was withdrawn under increased pressure. In 3 of the specimens the cell count was 12, and in 1 it was 10. In 3 there was a reducing substance present; in all 4 the globulin test was negative. These few cases are not included with the idea that any conclusions might be drawn from such a limited number, but that they might form a nucleus to which could be added cases of other observers.

It may be noted that the cerebrospinal fluid was essentially

negative in 3 of the cases. The details of the case with abnormal cerebrospinal fluid are as follows: No. 17,924, aged twenty-eight months, was admitted because of high fever (temperature 105.4 F.), persistent vomiting and diarrhea. The child was highly irritable; the knee jerks were exaggerated; there was no rigidity of the neck. The leukocytes numbered 42,000. The cerebrospinal fluid was withdrawn under increased pressure and showed 12 cells per c.mm., 75 per cent of which were polymorphonuclear leukocytes. The reaction for a reducing substance and globulin was negative. A culture of the cerebrospinal fluid was sterile. Status lymphaticus, fatty liver, and subpleural hemorrhages were found at autopsy. The preponderance of polymorphonuclear leukocytes may possibly be explained by an early invasion of the meninges, which might have developed into pyogenic meningitis had not death been caused by the associated status lymphaticus. This explanation does not go well with a sterile cerebrospinal fluid.

**Summary.** In acute respiratory infections the cerebrospinal fluid is usually normal. In certain cases which had an uninterrupted convalescence without sequelæ the cerebrospinal fluid showed a pleocytosis with or without a positive globulin reaction during the acute stage of the disease. It is believed that in certain of these cases the diagnosis of serous meningitis might be entertained. In 15 of these cases of pneumonia convulsions were present. In many of the cases from the other groups convulsions were also noted, yet in only a few was a pleocytosis associated with the presence of convulsions.

In acute and chronic intestinal conditions in infancy and early childhood the great majority of cases have a normal cerebrospinal fluid while a minority show a fluid with a slightly increased cell count.

In all the cases of tetany the cerebrospinal fluid was essentially normal; a small number only (5 of 31) showed a fluid with an average cell count of 21. An important observation regarding the patients with tetany was the low average cell count in a group of cases in which all but 5 had convulsions. This is fairly conclusive evidence that even repeated convulsions, which were observed in many of these cases, bear no relation to the number of cells in the cerebrospinal fluid.

In a group of 4 "neuropathic children" all had normal cerebrospinal fluids. In 1 of these the number of cells reached the upper normal limit.

Evidence is offered that there is no increased cell count in cases of acute otitis media by the findings in 8 cases with an average of 5.6 cells per c.mm.

It would appear from the variable findings in 4 cases of cerebral thrombosis that there is nothing pathognomonic in the cerebrospinal fluid.

The cerebrospinal fluid in congenital syphilis is clear and colorless (excepting in certain cases of syphilitic meningitis), and usually under normal pressure. The cytology is a variable factor. There is some evidence in this series of cases to demonstrate that there may be involvement of the central nervous system without a pleocytosis. The intensity of the clinical manifestations is apparently not a criterion to the cytology.

In cases of brain tumor one is impressed by the variable cerebrospinal fluid findings. In 11 of 21 cases the count was not higher than 10 cells per c.cm. In 7 cases the count was more than 100. In 15 cases tested for globulin only 6 were positive.

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### THE VALUE OF CRANIAL DECOMPRESSIVE OPERATIONS.

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THIS communication summarizes the observed effects of the various forms of cranial decompression as determined by a study of the clinical material admitted to, and operated upon in the surgical service of Mt. Sinai Hospital since 1915. The indications for this general form of operation have included tumor of the brain (approximately 78 per cent) and cranio-cerebral injury (approximately 11 per cent). Eighty-nine cases were studied. The general statistical information is as follows:

	Cases.
Decompression in all types of cases with and without preceding exploration or other operative procedure . . . . .	89
Died . . . . .	45
Decompression for brain tumor with and without preceding exploration or other operative procedure . . . . .	70
Died . . . . .	29
Decompression for cranio-cerebral injury . . . . .	10
Died . . . . .	5
Decompression for disease, malformation, etc. . . . .	9
Died . . . . .	5
Subtemporal decompression with and without preceding exploration or other operative procedure . . . . .	41
Died . . . . .	22
Subtemporal decompression . . . . .	26
Died . . . . .	13
Bilateral subtemporal decompression . . . . .	3
Died . . . . .	1
Subtemporal decompression plus other operative procedure such as contralateral osteoplastic flap, etc. . . . .	15
Died . . . . .	9
Suboccipital operations; decompression <sup>1</sup> always following exploration . . . . .	27
Died . . . . .	13

The patients in this series generally presented a comparatively poor operative risk. This was due to a deterioration of the general resisting powers of the individual produced primarily by the presence of a long standing intracranial lesion; and secondarily by the association of some other disease, notably, cardiovascular disease. The operations done upon these patients were performed by a number of different surgeons at the hospital.

The mortality following the operation is naturally in direct proportion to the gravity of the indication. In a small number of cases of inflammatory and degenerative disease, in whom the decompression was done under error of diagnosis, the mortality was highest. In cranio-cerebral injuries the gravity of the injury determines the mortality figure absolutely; and inasmuch as decompressive operations are not done for injury except when the latter, or its effects, is most severe, the mortality is, naturally, very high. Irremovable or unlocalizable tumors of the brain showed the lowest general immediate mortality after decompression.

The mortality of cranial operations is, to a large degree, dependent upon the extent of the procedure and the amount of intracranial manipulation. The highest mortality occurred when the decompression was added to some other procedure, such as an osteoplastic flap on the contralateral side. In these patients the decompression was often added because no definite site of disease was demonstrable in the exploration and it was hoped that the added decompression would relieve the symptoms of increased intracranial pressure of brain tumor or cranio-cerebral injury. These were all, naturally, subtemporal operations.

<sup>1</sup> It is questionable how much decompression results from this operation.

In this series, the subtemporal operation failed more often to relieve symptoms or to prevent a fatal outcome than the suboccipital operation: The difference is due entirely to the fact that the risks of the subtemporal operation were more willingly assumed in far advanced cases of supratentorial disease than were those of the suboccipital operation in equally far advanced conditions in the subtentorial fossa.

The subjoined table<sup>1</sup> demonstrates that these cranial operations are better borne in the earlier periods of life. The table includes all types of decompressions practised either alone or added to a major cranial operation.

	Patients.	Mortality, per cent.
From 1 to 5 years . . . . .	5	25
5 to 10 " . . . . .	7	28
11 to 20 " . . . . .	9	44
21 to 30 " . . . . .	21	13
31 to 40 " . . . . .	9	44
41 to 50 " . . . . .	17	64
51 to 60 " . . . . .	4	75

In the brain tumor cases the length of time for which the lesion was present prior to operation seems to make little difference in the mortality provided the general condition of the patient is equally good. It is noteworthy that a proportionally larger mortality was present in the patients in whom the manifestations of neoplastic disease were present a relatively short time—a few weeks. The explanation for this state of affairs lies in the fact that such patients surely had the tumor growing for a much more considerable time without the exhibition of any subjective symptoms. Then some striking and dominating phenomenon occurred, such as coma, or a hemiplegia, or one or more convulsions, which brought the subject forcibly to the patient's attention at a time when the disease was relatively far advanced; at this late time any operation added but another overwhelming insult when the resisting powers of the individual were at a minimum or were entirely gone. In the earlier years the tendency to interfere in such patients was much stronger than now; since then the futility of operating in such cases is recognized. The pathological basis for this lies in the occurrence of some accident in the tumor, especially hemorrhage, leading to pressure upon some vital area.

The cause of death after decompressive operations performed for cranio-cerebral injury has always been the effects of a very grave injury possibly plus the shock of the operation; death always took place within a few hours. The primary cause of death after decompression when done for brain tumor is always a long continued grave intracranial lesion. In the cases in which some other

<sup>1</sup> The differences are not quite as marked as the figures would indicate because, as age increases, other complicating factors enter which must be taken into account.

intracranial procedure preceded the decompression, the former was a most important contributory cause. Puncture of the brain in infiltrating tumors deserves especial mention as in about 20 per cent of the cases in which it is done, death follows in from one one to two weeks from hemorrhage into the tumor.

Decompressions are of two kinds. In the one a temporary effect is wanted for the purpose of permitting some other procedure. In the other a more lasting effect is desired for the purpose of relieving some or all of the symptoms of tumor of the brain. A decompressive effect upon the brain can be produced in a variety of ways. In infants and young children with hydrocephalus resulting from obstruction in the aqueduct or fourth ventricle, in whom the fontanelles are still open, decompression can be accomplished by aspirating the ventricle directly through the space unguarded by bone. The opportunities for this procedure were, however, uncommon. Unfortunately, too, the effect is very temporary and the procedure must be repeated. An attempt was made to obviate the disability of repeated aspiration when the corpus callosum puncture was devised; while the effect of the latter is more lasting in the successful cases than simple aspiration, it, too, has a relatively short period of usefulness in many cases.

In doing an exploratory operation upon the brain, in which a cranioplastic flap is turned down, decompression can be effected by removing the bony part of the flap. In previous years, this was sometimes unavoidable owing to an excessive bulging of the intracranial contents; but with modern methods of diminishing intracranial pressure, the need for this is relatively rare. The deformity resulting from such an operation is a progressive one, becomes very marked and the underlying brain is unduly exposed to all kinds of traumata; so that this makeshift procedure in the fronto-parieto-occipital regions is very undesirable and is practically never done now if one can help oneself otherwise. This series includes no case of this kind. A somewhat similar, though, to be sure, a much less marked effect can be accomplished by biting away a small segment at one of the lower angles of the bone flap and leaving the underlying dural flap partially open; most operators do this. When well planned and executed there is in many cases very little deformity and the brain is not exposed to injury. For many years, there has been a tendency to employ this technic in some of the brain cases for decompressive purposes.

Ordinarily, however, the operations practised include only the standard forms of the subtemporal (Cushing) and the suboccipital operation. In the earlier years attempts were made in a few of the cases to enhance the effects of the decompression—most commonly the subtemporal variety—by doing in addition a corpus callosum puncture. In this series the results were poor, however, and this additional procedure has not recently been done.

The subtemporal operation is always done on the right side in left handed persons; ordinarily it is a unilateral operation; but in several patients a bilateral operation was done either in one or two sittings. The technic includes the following steps: (1) Usually a bow-shaped incision is made over the temporal fossa planned and executed to avoid the temporal artery and the frontal and orbicular branches of the facial nerve; in rare instances a vertical incision is made; (2) division of the temporal fascia and muscle in a vertical direction adequately to expose the entire temporal fossa; (3) opening of the skull with a hand trephine and the enlargement of the opening by undercutting with appropriate forceps so that it measures finally 5 by 7 cm. as a minimum; (4) opening of the dura by a crucial incision and leaving it wide open at the conclusion of the operation; (5) careful suture of the outer wound.

In the suboccipital operation the usual cross-bow incision is made. The soft parts and muscles are pared from the bone and the subtentorial fossa is opened into on either side of the mid-line with a hand trephine. Enough bone is removed with rongeur forceps to adequately expose the cerebellum. This includes all of the flat surface of the occipital bone lying between the grooves for the lateral sinuses and the margin of the foramen magnum; the margin of the latter is always excised as soon as possible in order to prevent any sudden strangulation of the medulla. Latterly, the bone is removed well into the mastoid; the limit of this extension is the site of emergence of the stylomastoid artery from its foramen. The dura is opened from side to side across the median line and vertical incisions are added at either side up to the transverse sinus.

**DECOMPRESSION IN BRAIN TUMOR.** A certain amount of exploration is often done in the general area of the operative field. Subtemporal operations are done purposely as decompressive procedures; suboccipital operations always begin as explorations and when no disease is demonstrable, the results of the procedure serve although not done with this object in mind, for decompressive purposes. When there is very great increase in intracranial pressure and the brain substance prolapses into the opening of the dura, exploration is not possible. With modern technic attempts are always made to prevent this by emptying the ventricles as a preliminary measure; not always is this, however, successful both because the ventricles may contain only an insufficient amount of fluid, or, in rare instances, because the exploring needle escapes entering the ventricle. When much fluid can be removed from the ventricles, or, in certain cases, from large cystic collections due to the breaking down of the tumor, the manipulations are rendered much more simple and a fair amount of exploration can be accomplished; a greater degree of decompression is also assured in such cases. In the cerebellar cases emptying of the cisterna



magna is a great additional aid. Although our experience is small we have seen no beneficial decompressive effect resulting from the administration of concentrated solutions of sodium chloride.

In the earlier years the operations were practically always done under general anesthesia. It has latterly been recognized that this is a distinct disadvantage: The anesthetic drug increases the intracranial tension and adds more difficulty and danger to the intracranial manipulations; anesthesia carries with it, among other things, the dangers of postoperative pneumonia. So that, more and more, resort is being had to local anesthesia. As a general rule the patients tolerate this form of analgesia remarkably well and the operations can be satisfactorily done.

In the subtemporal cases the amount of shock or other appreciable effect is at a minimum. In the suboccipital cases the effect is much more pronounced. The fall of blood-pressure is sometimes considerable even in patients who are in very good general condition before the beginning of the operation; sometimes the pressure falls to 60 or 70 mm. Hg. by the time the dura is exposed; this happens in the absence of any loss of blood and is apparently explainable by the relatively larger extent of the surgical procedure and by the difference in location of the site of operation and its proximity to the vital medullary centers. The much longer time necessary for the performance of the suboccipital operation, as opposed to that necessary for the subtemporal operation, and the proportionally greater exhibition of anesthetic, when the latter is employed, is a powerful contributory factor in the production of shock in the suboccipital operation.

The manipulations necessary for the performance of either the subtemporal or suboccipital operation, in cases in which there already preëxists considerable increase of intracranial pressure and bulging of the brain, are ready causes for the production of variable degrees of edema of the brain. So that sometimes the patients' general condition shows some deterioration and individual symptoms show some increase in the first twenty-four or forty-eight hours after operation. Thereafter as the edema disappears and the static conditions in the cranium become accustomed to the new changes, the symptoms subside and improvement begins to be perceptible in those cases which are favorably influenced by the operation.

In a few of the cerebellar cases it was noted that following the operation a variable degree of rigidity of the neck was present in the first twenty-four or forty-eight hours after operation. It seems reasonable to assume that the latter was due either to the operative trauma in the musculature of the neck and the early stages of the consequent reparative inflammation necessary to the healing of the wound, or to some extravasation of blood. Somewhat similar phenomena to the last are present in cases of fracture

of the base of the skull; these are due to irritation of the meninges with blood; they were referred to in a previous communication.

There has been no case of brain tumor in this series in which there has been a complete disappearance of all of the elicitable neurological disturbances following a decompressive operation. There has been no case of brain tumor in this series in which, following the decompression, the relief of the subjective symptoms continued for a sufficiently long time to warrant the opinion that the lesion existing in the brain had remained stationary because of the operation. For these opinions it must be remembered that some of the neoplastic lesions are of extremely slow growth and that the palliation may continue unbroken for a number of years. From the point of view of the patient, palliation is sought for certain very perceptible and incapacitating disturbances, such as headache, disturbance of vision or speech, convulsions, paralyses or muscle weaknesses, and when such gross disabilities become lessened or disappear after operation, and the disappearance becomes noteworthy by its apparent persistence, it is assumed by the patient that a cure has been attained. From the point of view of the neurologist the assumption may not be justified because the previously existing abnormal neurological phenomena may continue to show progress, or new disturbances of neurological function may appear and grow more pronounced which indicate only too well to the neurologist that more and more brain tissue is becoming involved by the growing tumor.

Generally speaking 43 per cent of the cases of brain tumor subjected to decompression and in whom the operation was successfully carried out, were not relieved by the operation and left the hospital in an unchanged physical condition. Twenty-four per cent were only slightly benefited; 20 per cent were moderately benefited; 14 per cent were markedly benefited. After the subtemporal operation 23 per cent showed no change; 14 per cent showed only a slight improvement; 20 per cent a moderate improvement; and 7 per cent a marked improvement. After the suboccipital operation 10 per cent were slightly improved and 7 per cent were markedly improved. These figures are classified in the table for clarity:

	Subtemporal decompressions, per cent.	Suboccipital operations, per cent.	Total per cent.
Unchanged . . . . .	23	20	43
Slight relief . . . . .	14	10	24
Moderate relief . . . . .	20	..	20
Marked relief . . . . .	7	7	14

The determination of these percentage figures is based upon the general manifestations of brain and such outstanding subjective and objective symptoms as were indicated previously (headache, vision, convulsions, etc.). The proper comparison of the relative

importance of the various symptoms, their proper evaluation as compared with one another and from one case to the other, and their proper integration has been especially difficult. It is believed, however, that the figures are essentially correct and reflect the true state of affairs.

The differences in the various grades of relief which decompression has afforded have been more marked in cases of supratentorial neoplastic disease and after the subtemporal operation than with subtentorial disease and after the suboccipital operation. As a matter of fact after the suboccipital operation the postoperative improvement is either very marked, or so slightly marked as to make the separation of a group of "slightly relieved" cases more or less artificial.

Other things being comparably equal the good effect of a suboccipital operation, if the latter do exert a decompressive effect, is apt to be much more pronounced than that of a subtemporal operation. The difference is probably due to the fact that with subtentorial neoplastic disease the relative smallness of the posterior fossa, as compared with the cerebral, compels an earlier recognition of the disease and the performance of the operation at a time when the recuperation is more quickly and outspokenly possible and when mechanical disabilities are more easily correctable; the reverse is true with the supratentorial cases.

**EFFECT OF DECOMPRESSION ON THE GENERAL EFFECTS AND SYMPTOMS OF BRAIN TUMOR.** Intracranial compression in brain tumor is, generally speaking, a slowly developing phenomenon. Far-reaching effects may, therefore, develop and continue for comparatively long periods of time; in this regard the phenomenon is vastly different from the quickly developing compression following cranio-cerebral injury. The exceptions to this rule are, however, not very uncommon. Then signs of compression appear quickly chiefly because of hemorrhage into the brain or tumor substance or into the ventricle; the symptoms include rapidly progressing stupor, increase in the papillo-edema, slowness of the pulse, etc. The ordinary slow form of compression is variously influenced as indicated subsequently in this communication. With acute forms of compression complicating tumor of the brain, especially in the variety in which hemorrhage occurs into the ventricle, the ordinary forms of decompression exhibit no benefit; the usual course of affairs includes a continual progression of the picture and exitus follows fairly rapidly.

The condition of the brain substance as exposed in the operative field has important bearings on the appearance of any subsequent good effect of the decompression in cases of neoplastic disease. There may be one of two conditions:

1. In one variety the brain is under a variable degree of tension under the unopened dura. In the most extreme of these the

degree of tension is such that there is very little, if any, give to the exploring finger as it presses on the dura; there is no pulsation. The slightest nick in the dura causes an instantaneous extrusion of brain tissue; a larger incision is followed equally rapidly by the progressive prolapse of the exposed brain substance, so that very quickly it forms a large projection above the surface of the dura. In the severe cases the cortex is anemic. In the moderate cases the surface of the brain has a deeper tint than normal, has a glazed appearance, is covered with dilated and distended pial vessels and feels firmer to the finger than it normally should. The tissue is extremely fragile. Bleeding occurs very readily at the slightest touch, or occurs spontaneously. At any manipulation, or in the extreme cases without any, the surface of the cortex fissures and ruptures and, very quickly, the brain substance becomes dark red and disorganizes completely, so that the characteristics of normal brain tissues are lost. These phenomena are more frequently seen in the subtemporal cases. In the latter there is consequently much difficulty in properly closing the wound. These changes are due to interference with the circulation in the cortex.

2. In other cases there are none or, at most, very little of these changes owing to the fact that there is no increase in intracranial pressure. In fact the gross appearances of the brain are those expected in normal individuals. In a very few I have thought that there was less than the normal present both as regards the relative size of the brain to its containing bony case and as regards the tension under which it functionates.

One would expect that the first of these two groups would contain the cases in which the maximum amount of good would follow the decompression. As a matter of fact, however, this is not so. It is very remarkable that the second group—those with very little, or no increase in intracranial pressure and with very little macroscopical change in the operative field contains the cases in which beneficial effects are more frequently seen. This is especially apt to occur with the subtemporal decompression cases.

The explanation of this phenomenon does not seem quite clear. In those with marked increase of intracranial pressure a possible explanation exists in the following. The increased tension and marked bulging of the brain is caused by an increase in the total cubic content of the brain (1) either because of simple swelling (Reichard), or hyperplasia (Spiller) accompanying an infiltrating type of tumor; or (2) because of the internal hydrocephalus; or (3) by varying proportions of both of these causes acting together. The increased intracranial pressure is due to an expansive force acting from the interior of the brain; and especially in the cases of internal hydrocephalus any relief which occurs is more than counteracted by an increased accumulation of intraventricular fluid. When the possibility exists of recognizing this state of affairs

before operation, the futility of doing subtemporal decompression is now recognized. In these cases of internal hydrocephalus good results can sometimes be obtained by doing a corpus callosum puncture.

I hazard the following explanation for the other cases—those with no bulging of the brain and with apparently no evident macroscopical change in the operative field. Possibly, in these cases the increased intracranial tension is due to some agency working externally to the brain—between it and the cranium. Possibly this agency is an increase in the amount of cerebrospinal fluid; not much would be needed to disturb the intracranial static conditions as brain tissue is physically incompressible. Such a mechanism would explain adequately, also, the appearance, referred to previously, in which the brain has given the impression of being slightly smaller than it ordinarily should be. The removal of a segment of bone and the opening up of the dura could, under such conditions, exert a very appreciable effect. I give the notes of one case in which, it seems to me, this viewpoint is corroborated by the postoperative facts.

In a patient with well marked general symptoms of brain tumor including a moderate grade of optic neuritis and extreme headache, the typical subtemporal decompression was done. There was no macroscopical evidence in the operative field of any increase of intracranial pressure and no bulging of the brain. However, an immediate marked beneficial effect followed including the complete disappearance of the headache. No appreciable bulging of the soft parts over the site of the decompression followed for some time. Then the area gradually began to bulge and the swelling grew larger and very tense and coincidently with this development the headache returned and grew progressively more marked. The bulging was due to an accumulation of cerebrospinal fluid and when the latter was removed by aspiration, the headache promptly disappeared, only to reappear once more as the fluid reaccumulated. This was repeated several times. The symptoms were unquestionably due to brain compression produced by a force acting from without.

The effect of intracranial compression has a direct and proportional relation to the competence or poverty of the general condition of the patient as determined by the condition of the circulation and the general state of the vital functions; these are not impaired appreciably in cases of brain tumor except when the compression is marked and has existed for some time; these usually indicate secondary effects on the medullary centers. After decompression any rehabilitation of these centers and any improvement in their functions are in direct proportion to the degree of decompressive effect.

*A. Effect of Decompression on Stupor and Drowsiness.* Four of the patients in this series were deeply unconscious, stuporous or comatose prior to the decompressive operation. Two of these were unlocalized cases of brain tumor; 1 had a tumor in the frontal region; and the fourth had a tumor of the thalamus. One of these (thalamic case) improved remarkably; 2 others were not benefited at all and died very shortly after operation; the fourth was removed from the hospital against our advice in a comatose condition, the operation not having been followed by any improvement, and, presumably died later at home. The first 3 were subtemporal, the last was a suboccipital operation. In our cases the stupor or coma had appeared fairly suddenly and had precipitated the operation. The experience seems to show that as a general rule a decompression will not influence a suddenly appearing stupor and that the latter can be classed in the great majority as an ante-mortem or terminal phenomenon of tumor of the brain. In an isolated case, however, a good effect can be obtained. The notes of one case may be of interest:

Hospital No. 154,635. A woman, aged fifty-five years, had the general symptoms of brain tumor. The symptoms included: (1) Marked headache; (2) marked rigidity of the neck; (3) marked Kernig; (4) weakness of the right facial nerve of the thalamic type; (5) weak knee and ankle jerks. Lumbar puncture demonstrated increased tension to the cerebrospinal fluid. The Wassermann reaction was negative. There was a papillo-edema of one diopter. The patient was unconscious though not as deeply stuporous as in the fatal cases referred to previously. Following a right subtemporal decompression there was marked improvement and the patient was able to be up and about the wards. The facial weakness lessened; the rigidity of the neck and the Kernig disappeared.

Six other patients of this series exhibited various states of drowsiness; 1 had a tumor of the pineal gland and 1 of the frontal region; the others were cases of unlocalized tumor. The pineal patient showed no improvement; the frontal patient showed a slight grade of improvement so that questions could be answered even though with difficulty. In the others the drowsiness deepened to stupor and in 2 of these, explorations were done at a later period. In general the experience is not encouraging in regard to the effect of decompression on this symptom. The fact that there was a tendency in these cases for the drowsiness to deepen to stupor probably indicates that, as a general rule, the symptom is one which is not relievable by decompression and is a forerunner of deeper states of coma or stupor appearing as terminal phenomena of tumor of the brain.

There was 1 case of hypophysial tumor in the series in which drowsiness appeared as a new symptom after a subtemporal decom-

pression. There were other evidences of endocrine disturbance in this patient, including an amenorrhea; and I think that the drowsiness was probably related to the endocrine malfunction and was not an effect of the decompression.

*B. Headache.* In 43 per cent of the cases of subtemporal decompression, in which the operation was successfully carried out, the headache, which had been present before operation was not relieved; in 37 per cent it was partially relieved and in 18 per cent it was wholly relieved. In 20 per cent of the suboccipital cases, in which the operation was successfully carried out, the preëxisting headache was not relieved; in 40 per cent it was partially relieved and in 40 per cent it was wholly relieved. Headache is the one symptom which the patients complain of mostly and any improvement is very welcome. Fortunately headache is relieved, either partially or wholly, in a large proportion of the cases of brain tumor that are decompressed. Our statistics show that the symptom is more often relieved in cases of subtentorial, than in cases of supratentorial disease; and it corroborates the statement, made in the earlier part of this communication that the suboccipital cases are more apt to have the subjective symptoms relieved than the subtemporal cases.

*C. Effect of Decompression on Mentality.*<sup>1</sup> In the cases of brain tumor in which the clinical picture led us to suspect that the lesion lay in the frontal areas, decompressive operations had no effect upon the character of the disturbances of mentality and personality.

2. EFFECT OF DECOMPRESSION ON FOCAL SYMPTOMS. *A. Effect of Decompression on Spasticity.* Spasticity of some portion of the body was a prominent symptom in 6 of the patients. In 1 the right side of the body was held rigid; in a second a similar phenomenon was present at times and was associated with a temporary loss of speech. The first of these patients died after operation; the second was not improved. In the 4 other patients there was marked rigidity of the neck. Two of them had unlocalized tumors; both died after operation. In another, the tumor was in the posterior fossa and the spasticity was not relieved by the decompression. The fourth was a patient with a frontal lobe tumor; the rigidity of the neck promptly disappeared after operation and the patient's general condition was markedly improved. It appears that as a general rule spasticity is a rather unfavorable symptom and is not usually relievably by decompression. Except for the fact that the decompression resulted in a general relief of intracranial pressure, I have no explanation to offer for the good effect noted in the one case as opposed to the uniform absence of effect seen in the other cases.

<sup>1</sup> Changes in mentality are classified in this communication as general symptoms. It is to be remembered, however, that the symptom is frequently utilized as a contributory factor in the localization of a tumor in the frontal regions.

*B. Effect of Decompression on Convulsions.* One of the patients in this group was subject to epileptic seizures for twelve years prior to the onset of the symptoms of brain tumor. Another had generalized epileptiform convulsions only during the period in which the symptoms of brain tumor were present. A third patient had convulsive seizures limited to the right side of the body. A fourth patient had attacks of rigidity limited to the right side associated with loss of speech; later he developed convulsions.

In 2 of these patients fatalities occurred, the reason for which probably lay in the fact that an extensive exploration had preceded the decompression. In the others there was no improvement in this symptom. In this series of tumors of the brain, this symptom was not relieved by decompression; this agrees with the usually held view in regard to the effect of any form of operation upon well established epileptiform conditions.

*C. Effect of Decompression upon Muscular Weakness and Paralysis.* There were no cases of monoplegia or diplegia in this series of brain tumors.

There were 10 patients in whom a more or less pronounced weakness or paralysis of one side of the body was one of the symptoms of the clinical picture. Three of them died after the operation, 4 were entirely unrelieved and the remaining 3 were markedly benefited by the decompression. One of the last had had, originally, a spasticity and, in him, a change to a hemiplegia occurred as a sudden phenomenon; the promptness with which the decompression was done in this patient probably had much to do with the relief of the symptom. In our experience, when the patient is in good general condition and the weakness or paralysis has not been of too long duration, beneficial effects may be expected to follow a decompression.

*D. Effect of Decompression on the Reflexes.* In patients with brain tumors the condition of the reflexes follows no essential rule. Frequently, indeed, they correspond in the orthodox manner to the character of the lesion; but, just as often, the reflexes show an alteration of activity, which may or may not be equal or unequal on the corresponding sides of the body and for which change no explanation is entirely satisfactory. In a similar manner abnormal reflexes are present or absent. After decompressive operations the experience goes to show that a similar absence of uniformity makes it difficult to draw deductions that would be of value in clinical neurological surgery. The condition of the reflexes present after operation, as differentiated from the condition present before operation, may show wide variations in both directions; and changed conditions of normal reflexes, or abnormal reflexes appear as new phenomena when they were not present prior to operation. Interpretations are made very difficult because the changed pressure conditions within the cranium resulting from the decompression are, in themselves, capable of producing these variations of the



reflexes aside from the presence or progression of the neoplastic lesion.

*E. Effect of Decompression upon Sensory Changes.* Sensory changes of one kind or another were present in a fair proportion of the cases of brain tumor; the changes varied from well defined areas of changed or absent sensation (fifth nerve distribution) to hemianesthesias. There were 5 patients in this series in whom these sensory abnormalities were present. One of these died following the decompression, 3 others showed improvement—in 1 of them the improvement was marked. The fifth was not improved. Taken by itself this symptom has little importance, but as a contributory factor in the entire clinical picture this class of symptom helps in the determination of the good, bad or want of effect of the decompression.

*F. Effect of Decompression upon Aphasia.* Eight patients were decompressed in whom some form of sensory or motor aphasia was prominent in the symptom-complex of brain tumor. Five of them died following the decompression; in all but 1 right-sided subtemporal operations were performed; in the exception, a suboccipital operation. In 1 of the patients the brain bulged considerably after the dura was incised. In all of the others, there was no marked abnormality to be seen in the operative field. Two of the patients who survived the operation were not relieved in any way; 1 was only moderately improved. In the patients of this series aphasia was generally associated with far advanced neoplastic disease of the brain; this explains the high mortality. Our experience indicates that the various forms of aphasia, both sensory and motor, are relatively little influenced by decompressive operations.

*G. Effect of Decompression upon Cranial Nerve Involvement.* Various grades of involvement of the different cranial nerves are common in the symptom-complex of brain tumor. Very slight changes in some of them are, frequently, evidence of generally changed intracranial conditions, whether these be due to tumor or to other lesions. Such slight changes are, apparently, not influenced by decompressive operations. When the cranial nerves are more markedly involved, they, of course are indicative of focal lesions, and help in the localization of the tumor. As will be shown in what follows; these are variously influenced by decompressive operations.

(a) *Effect of Decompression on Vision, Papillo-edema and Optic Nerve Atrophy.*<sup>1</sup> Eye symptoms are common in cases of tumor of the brain. In 18 of the patients of this series there were various grades of loss of vision in one or both eyes up to complete blindness and all of the patients had various grades of papillo-edema. Three of the patients died after operation; 6 were unimproved;

<sup>1</sup> For purposes of convenience, all eye symptoms are grouped together in this communication, although some of them are of a general nature,

3 were slightly improved; 1 was moderately improved. In 1 patient there was depreciated vision in only one eye which was greatly improved by the decompression.

In 2 patients there was an hemianopsia. One had, in addition, diplopia; and as a subtemporal operation did not benefit him and because posterior fossa symptoms developed, a suboccipital operation was performed with fatality. The second patient with hemianopsia was greatly improved by the subtemporal decompression. One patient, who was blind in one eye, was not relieved by the decompression. These cases show that the vision of many of the patients was markedly benefited by decompressive operations; those, who were, were usually the ones who had had failing vision for comparatively short periods; in those who were not improved, failing vision was present for a long time and the accompanying neuritic atrophy was unrelievable.

In brain tumors loss of vision is due either to direct pressure upon the visual pathways or to optic neuritis. Papillo-edema was present in 22 patients of this series, and varied from a slight blurring to a swelling of 6 diopters or more. In some, the papillo-edema appeared quickly under observation in the hospital and rapidly advanced to an extreme degree; in another group, the patients came into the hospital with a high grade of choked disc, which either did not vary appreciably from day to day, or showed tendencies to increase. In the last group the assumption was that the papillo-edema had been present for a considerable period of time.

Of the 22 patients, 8 died after the decompression. In 7 patients, in most of whom the symptoms were of long duration, the swelling of the discs did not diminish after the decompression during the period they were under observation (from three weeks to three or four months). Only occasionally will a long-standing papillo-edema lessen considerably after operation. In 5 of the patients, usually the more recent cases, there was considerable improvement. In 1 patient the swelling grew more marked after the decompression. As a general rule in those who are benefited after the decompression, the swelling recedes slowly and very soon reaches a stationary stage from which it does not vary appreciably. In a few, improvement is more rapid and the swelling disappears completely.

The facts regarding papillo-edema are shown more in detail in the appended table:

Preoperative condition.		Postoperative condition.			
Degree of nerve swelling.	Total number.	No improvement.	Improvement.	Increase.	Died.
Blurring . . . .	1	..	..	..	1
1 diopter . . . .	5	3	1	..	1
2 diopter . . . .	4	..	1	..	3
3 diopter . . . .	2	..	1	1	
4 diopter . . . .	5	3	..	..	2
5 diopter . . . .	1	1			
6 diopter . . . .	1	1			
"Plus" . . . .	2	1	1		
"2 plus" . . . .	2	1	1		

The amount of secondary atrophy of the discs, that already exists, is as is well known never lessened by the decompressive operation. This holds true even for those cases in which the changes are apparently at their very beginning when the decompression is done. When diminution of vision is due to advanced optic atrophy the disability may become more marked and may end in blindness even after a satisfactorily completed decompression. Because of the varying degrees of optic atrophy that are present, the improvement, or lack of improvement in vision which follows a decompression does not always correspond with the changes in the swelling of the discs.

(b) *Effect of Decompression upon Oculomotor Disturbances.* There was only 1 patient in this series with ptosis. There was no change after decompression either for the better or worse.

There were 6 patients with disturbances in the fourth and sixth nerves leading to various degrees of strabismus with diplopia. Two of the patients died; they were both cases of unlocalized tumor. A subtemporal operation had been done in 1; in the other a subtemporal decompression was later followed by a suboccipital operation. Two other patients with unlocalized tumors, were very much benefited by subtemporal operations. In the fifth patient the symptoms pointed to an involvement of the left thalamus and a subtemporal operation was followed by marked improvement. The sixth patient had subtentorial symptoms and was much improved by the operation.

Nystagmus was noted in 11 of the patients of this series; 5 of them were cases of cerebellar tumor, 1 of mid-brain tumor, and in the others, the tumors were unlocalized. Two of the patients with cerebellar tumor died. Nystagmus sometimes appears in the picture as an item of indefinite value and seems to be related to the general pressure disturbances within the cranium. In subtentorial disease, however, it usually has diagnostic significance. The influence of decompression upon the nystagmus was the following: In 3 cases there was no change, in 3 others there were various grades of improvement, in 1 the character of the nystagmus changed after operation, and in still another, a fine nystagmus appeared where none had been present before operation. Even in the cerebellar cases, in which this symptom is most apt to be present, there does not seem to be any definite relationship between the nystagmus and any improvement or lack of improvement which follows the decompression. Taken alone this symptom cannot be taken as a measure of the relief afforded by the operation; taken in combination with other elicitable data, it furnishes contributory evidence of the success or lack of success of the decompression. There is no absolutely reliable interpretation with which one can regard the symptom when it reappears as a new factor after decompressive operations.

(c) *Effect of Decompression upon Eighth Nerve Symptoms.* Deafness was present in 2 cases of cerebello-pontine angle tumor without any vestibular changes. Unfortunately, both of these patients died and no deduction can be made regarding the effect of decompression. There was 1 patient with vestibular changes in whom the condition remained unchanged after operation.

A very remarkable case was the following:

In a young boy with the symptoms of subtentorial brain tumor a suboccipital operation demonstrated a cyst of the cerebellum. The operation was practically a decompression. There was relief from the symptoms for more than a year after which the patient returned to the hospital with his old symptoms and the functional tests pointed to changes in the vestibular apparatus. The cyst was then aspirated through the area of bone defect with an immediate disappearance of his symptoms and a change to the normal in the vestibular apparatus as demonstrated by a repetition of the functional tests.

The observation is of value in indicating how, in specially favorable cases, one can prolong the good effects of a decompression. In cases of cyst or of internal hydrocephalus the reaccumulation of fluid causes a return of the symptoms of compression. The withdrawal of the fluid results in a corresponding relief of the symptoms.

In the cases of brain tumor in this series in which major focal symptoms were a part of the clinical picture, our experience shows that little hope of benefit may be held out to result from decompressive operations. Usually the disease is very far advanced, or its effects of so profound a nature as to lead to a fatality in many and to no benefit to the largest proportion of those who do not succumb.

DECOMPRESSION FOR CRANIO-CEREBRAL INJURY. The value of the various forms of operative treatment in cranio-cerebral injury were summarized in a previous communication.\* From the point of view of the neurologist, as well as of the general surgeon, the opinion seems sound that conservative and expectant methods of treatment, whenever they can be safely employed, yield the best general results. We are unalterably opposed to operating indiscriminately upon all patients with cranio-cerebral injury. As the cases present themselves for treatment they seem to fall into one of three groups: (1) A large group the members of which always recover spontaneously; (2) a smaller group the individuals of which are almost certain to die with or without operative treatment and in which any form of treatment is futile; (3) a very small group in which the individuals present such border-line evidence as to make a policy of watchful expectancy advisable, but for whom one

\* Wilensky, Am. Surg., October, 1915.

should be constantly on guard and in readiness to operate at a moment's notice. The final outcome in the individuals in the last group is always doubtful.

Irritative or paralytic focal symptoms which point to pressure upon definite cortical areas are important indications for operative interference. Isolated or irregular disturbances of neurological function existing alone in the absence of evidence pointing to involvement of definite brain areas do not constitute an indication for operation. They undoubtedly indicate some brain lesion the effects of which are of only a temporary nature and are recoverable from, or can be compensated by newly assumed functions in other regions of the brain. When the need for operation exists because of definite focal symptoms, the indication is to do an exploratory procedure over the suspected area and to rectify the pathology, if possible. When, as is most commonly so, the latter is a blood clot or depressed bone, beneficial effects are customarily seen and the symptoms promptly disappear; otherwise the operations are futile. In either case after left-sided explorations, contralateral subtemporal decompressions might conceivably be indicated to obviate the effects of any brain edema existing previously because of the original trauma, or occurring subsequently to operation as a consequence of the latter itself.

Focal symptoms, the causes for which are not demonstrable or removable during an exploratory craniotomy are not influenced in the slightest degree by decompression alone. They are usually due to destructive lesions of brain tissue and divisions of nerve trunks. This was well illustrated in one patient in whom the injury resulted in total blindness undoubtedly due to division of the optic nerves; a subtemporal decompression had absolutely no effect and the patient remained blind.

Operation is imperative in every case of cranio-cerebral injury which shows the signs of an advancing intracranial compression. Operation should be done in the early stages before there is evidence of medullary involvement. The nature of the procedure is determined by the suspected character of the injury and of its effects. Exploration is needed when hemorrhage is suspected in order to stop the bleeding and remove the accumulated blood, this being the commonest cause for a rapidly advancing compression. When the compression is due to massive brain edema the indication would be met by a decompressive operation. Frequently the differentiation is not possible, nor the side of the head which harbors the major lesion; in these a button of bone should be lifted out on the left side and if no accumulation of blood is found either outside or underneath the dura, a right-sided subtemporal decompression should be done. The prognosis is good in the milder cases, but small in lesions which cause extreme brain edema and compression; the latter are usually fatal.

In the cases of cranio-cerebral injury in this series, in whom decompression was done, the operations were performed in all but one of the cases for extremely urgent indications (compression) within a few hours of the injury. In an isolated case, the patient continued in stupor for five days without any apparent advance in the signs of compression; then, because there was a marked fall in the blood-pressure, the decompression was done with a fatality within a few hours.

In a previous communication<sup>1</sup> the value of lumbar puncture as a decompressive measure in cranio-cerebral injury was summarized. Experience showed that when the intracranial compression was of a high grade, lumbar puncture had no decompressive effect and other more active measures were sometimes necessary. In mild cases of compression it has been difficult for us to say definitely that the release of fluid from the subarachnoid space by lumbar puncture had helped in the amelioration of the symptoms, because in some mild cases in which the procedure was not carried out, spontaneous improvement followed. The good results which Alhaique, LeRiche and Albert obtained with lumbar puncture and probably explainable on this basis. The experience of Cushing and Gray is more in accordance with our own.

DECOMPRESSION IN POST-TRAUMATIC EPILEPSY. There were 3 cases of epilepsy following cranio-cerebral injury, in whom decompressive operations were done. In 1, sufficient improvement followed the unilateral operations to warrant its repetition on the opposite side; the final result, however, was unsatisfactory. In another case with a depression near the median line at the vertex of the skull, the excision of the scar left a large opening which undoubtedly functionated as a decompression; in this case also no improvement followed. In another patient a subdural cyst was encountered which was drained through the decompression opening. The final result is not known in this patient.

In 1 case of epilepsy in a microcephalic child of twenty months, a considerable excess of cerebrospinal fluid was demonstrated at the decompressive (subtemporal) operation. Unfortunately the patient died of a meningitis. Our experiences with epilepsy have been small because the operations, for this indication, were done in much earlier times. Decompression is not now done for this indication.

In the earlier experiences decompressive operations were done in a few cases of Little's disease, and, perhaps under error, in cases of degenerative and inflammatory disease of the brain. The experience, however, was very small. Decompressive operations are not done for such indications now.

<sup>1</sup> Wilensky: Ann. Surg., October, 1919.

**Conclusions.** The mortality of decompressive operations is entirely dependent upon the gravity of the indication, the length of time the neoplastic disease had preëxisted and upon the general condition of the patient.

Generally speaking 57 per cent of the patients of this series in whom the operations were successfully carried out were relieved in greater or less degree.

Any beneficial effect of decompression upon the symptoms of brain tumor is not always proportionate to the degree of the preëxisting increase of intracranial pressure.

Many of the cases of brain tumor studied in this series were admitted to the hospital in the terminal stages of the disease in which both general and focal groups of symptoms were well marked. As a general rule, it may be said that under such disadvantageous conditions the results are not good, even though in exceptional instances unexpectedly good results are obtained, more especially in the general symptoms and to a less degree in the focal groups of symptoms.

In cranio-cerebral injury the indication for doing decompression is seldom present.

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## BACTERIOLOGY OF ACUTE RESPIRATORY DISEASE DURING AN INTEREPIDEMIC PERIOD, WITH A DISCUSSION OF CONDITIONS FAVORING STREPTOCOCCUS EPIDEMICS.\*

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DURING the winter of 1921-1922, the acute respiratory disease occurring in Philadelphia presented nothing of the epidemic character observed for these diseases throughout the United States during the winter of 1918-1919, so that an analysis of the bacteriological findings during the two periods appeared to be of especial interest in a study of the conditions determining the epidemic and the sporadic manifestations of acute respiratory diseases.

The findings presented for the more recent period represent the results of cultures made in the Bacteriological Laboratory of the Philadelphia General Hospital of specimens sent to the laboratory from the wards of this hospital treating acute respiratory diseases. They serve to indicate the nature of the acute respiratory infections in this hospital from October, 1921, to May, 1922.

\* Read before the Philadelphia Pathological Society, May, 1922.

**DIRECT CULTURES OF SPUTUM.** In 28 instances, direct cultures of sputum were made on beef-infusion blood-agar medium. These represent a miscellaneous group of patients, 11 of whom were diagnosed clinically as pneumonia, the remainder being divided among such diagnoses as: Common colds, acute bronchitis, influenza, bronchiectasis, lung abscess and gangrene of the lung.

The findings in this group were:

	Number of instances.	Per cent.
Pneumococcus . . . . .	12	43.0
Type II . . . . .	1	
Type IIa . . . . .	2	
Type III . . . . .	2	
Group IV . . . . .	7	
Hemolytic streptococcus . . . . .	12	43.0
Bacillus influenzae . . . . .	20	71.0
Streptococcus viridans . . . . .	18	
Micrococcus catarrhalis . . . . .	19	
Bacillus mucosus capsulatus . . . . .	2	

N.B.—By direct examination of stained preparations, spirilla were found in 2 instances and Bacillus tuberculosis in no instance.

The findings for the pneumococcus reveal particularly the failings of the direct cultural method, since with proper methods, an incidence of pneumococcus of from 20 to 25 per cent above the 43 per cent found here, can be demonstrated among normal individuals. The usual mouth types of pneumococci are shown in all except one instance, that of a pneumococcus Type II, so that, in view of the findings recorded in Table I, the findings presented above are certainly open to question from the standpoint of the reliability of the direct cultural method for demonstrating the pathogenic pneumococcus of a particular patient.

The direct culture method is more accurate for demonstrating hemolytic streptococci and Bacillus influenzae. A demonstrated incidence of 43 per cent for hemolytic streptococci and one of 71 per cent for Bacillus influenzae are significant findings in that they indicate that these organisms were lurking about in a large proportion of the acute respiratory infections. From the following tables an effort will be made to determine whether their presence was of as great a significance during this period as it was during the pandemic of influenza in 1918.

**PNEUMOCOCCUS TYPINGS IN PNEUMONIA.** Pneumococcus typings by the mouse method, with the sputa of 83 patients with pneumonia, gave the results recorded in Table I.

Type I pneumococcus occurred in about one-fifth of all the pneumonias, or in about one-fourth of the pneumococcus pneumonias.

This indicates a tendency to a return to the findings in pneumonia prior to the influenza epidemic.<sup>1</sup> The mouth types of pneumococci appeared here in a rather large proportion of instances. It must be remembered, however, that in this group were included



patients of all ages—many aged and suffering from chronic cardiac and kidney diseases—patients, in whom even an outstanding acute pneumonia is, in a sense, to be regarded as a secondary pneumonia. The high incidence of pneumococcus Type II (atypical), pneumococcus Type III and the inagglutinable Group IV pneumococci among such pneumonias is not surprising.

TABLE I.—PNEUMOCOCCUS TYPINGS—PNEUMONIAS.

	Number.	Total.	Per cent.
Pneumococcus Type I . . . . .	15		
Pneumococcus Type I and IV . . . . .	1		
Pneumococcus Type I and B. influenzae . . . . .	1	Type I.....17	20.5
Pneumococcus Type II . . . . .	3		
Pneumococcus Type II and III . . . . .	1	Type II.....4	4.8
Pneumococcus Type II, atypical . . . . .	3		
Pneumococcus Type II, atypical, and B. influenzae . . . . .	1	Type IIa....4	4.8
Pneumococcus Type III . . . . .	9		
Pneumococcus Type III and IV . . . . .	1		
Pneumococcus Type III and B. influenzae . . . . .	1	Type III....12	14.5
Pneumococcus Group IV . . . . .	31		
Pneumococcus Group IV and B. influenzae . . . . .	2		
Pneumococcus Group IV, Hemolytic streptococcus and B. influenzae . . . . .	1	Group IV....36	43.4
Hemolytic streptococcus . . . . .	5		
Hemolytic streptococcus and B. influenzae . . . . .	2	Hem. strep...8	9.6
B. influenzae . . . . .	4		
B. influenzae and Streptococcus viridans . . . . .	2	B. influenzae..14	17.0
Total . . . . .	83		

Hemolytic streptococci occurred alone in 5 instances; with pneumococcus and *Bacillus influenzae* in 1 instance; and, with *Bacillus influenzae* in 2 instances; in all, in 8 instances, or in 9.6 per cent of the specimens.

*Bacillus influenzae* occurred alone in 4 instances, and in combinations with pneumococci and streptococci in 10 instances—in all, in 14 instances, or in 17 per cent of the specimens.

BACTERIOLOGY OF EMPYEMA FOLLOWING PNEUMONIA. Of the 83 patients with pneumonia listed above, 4 developed empyema. Five other instances of empyema, in patients entering the hospital with this condition were included.

TABLE II.—BACTERIOLOGY OF EMPYEMA FOLLOWING PNEUMONIA.

Pneumococcus Type I*	1
Pneumococcus Type I and <i>Bacillus influenzae</i> . . . . .	1
Pneumococcus Type II*	1
Pneumococcus Type III . . . . .	1
Pneumococcus Group IV . . . . .	2
Pneumococcus Group IV and hemolytic streptococci . . . . .	1
Pneumococcus Group IV and <i>Bacillus influenzae</i> * . . . . .	1
Hemolytic streptococcus*	1
Total:	
Pneumococcus . . . . .	7
Pneumococcus and hemolytic streptococcus . . . . .	1
Hemolytic streptococcus . . . . .	1

\* Cases developing among the 83 pneumonias of Table I.

The noteworthy feature of the empyema following pneumonia was the predominance of pneumococci as the etiological agents. The one instance in which a hemolytic streptococcus occurred alone was in the case of a child developing otitis media, bronchial pneumonia and empyema complicating pertussis.

**Discussion.** In this hospital service, during the period of observation, hemolytic streptococci and *Bacillus influenzae* did not appear to play prominent roles in the pneumonia and in empyema following pneumonia. Neither organism appeared to be especially pathogenic for mice, since, in the pneumonia typings, these organisms did not "come through the mouse" in any great number of instances. This was in direct contrast to what was almost the rule for these organisms during the influenza epidemic. Again, while hemolytic streptococci were present in a considerable number of sputa on direct culture, the empyemas following pneumonia were for the most part due to pneumococci. This indicates a lack of power for invasion on the part of the hemolytic streptococci. The lowered pathogenicity for white mice and the lowered incidence of hemolytic streptococci in the empyemas following pneumonia, appear to indicate that both of these microorganisms had lost their powers to invade deeply a pneumonic process. During the 1918-1919 influenza epidemic, hemolytic streptococci had acquired a deadly power to invade. This was also true of *Bacillus influenzae*, which invaded the lung deeply, at times reaching the pleura, but rarely the blood stream in demonstrable numbers.

The question arises as to why the hemolytic streptococci and the influenza bacilli of the past winter differed in their abilities to produce complications in pneumonia, from that of their progenitors back in 1918-1919. What applies to one of these organisms may be said to apply to the other as well, so that this question may be answered if one explains why a hemolytic streptococcus in the natural exudates, or tissues of a person dying of a generalized streptococcus infection, upon direct inoculation into animals proves very fatal, while the same organism, after being grown even once in artificial culture, proves much less virulent. After a number of subcultures on a artificial medium, virulence is greatly lessened, but it can be restored in large part, by rapid, preferably mediate, transfer from one susceptible animal to another through a series of inoculations. For enhancing virulence by such a laboratory experiment, it is necessary that *the dose be massive at first*, that it sets up *an acute inflammatory process* and that *material from this acute inflammatory process at its height* be inoculated into the animal next in the series of transfers. In man, these conditions are fulfilled naturally by spontaneous transfer of infection during the building and maintenance of epidemics of acute respiratory disease.

**PREVALENCE OF HEMOLYTIC STREPTOCOCCI AS A FACTOR IN DETERMINING VIRULENCE.** In throat cultures of 64 men, upon their

assembly from outlying country districts in November, 1918,<sup>2</sup> hemolytic streptococci were not demonstrated in a single instance. By multiplying the methods of examination, so as to include direct sputum cultures and cultures of the peritoneal exudate of white mice inoculated intraperitoneally with sputum, among 50 of these men, 3 were shown to harbor small numbers of hemolytic streptococci.

Levy and Alexander<sup>3</sup> found among recruits arriving at Camp Taylor, that 14.8 per cent of them harbored hemolytic microorganisms (not definitely identified as streptococci). Contrasted with these findings, the same observers demonstrated an 83.2 per cent prevalence of hemolytic streptococci among healthy men in Camp Taylor. Irons and Marine<sup>4</sup> reported a 70 per cent incidence of hemolytic streptococci among healthy men at Camp Custer.

During the same periods, it was shown by a number of investigators<sup>5</sup> that among patients with measles, the incidence of hemolytic streptococci, as determined by throat cultures, was lowest upon admission to the hospital wards and increased with the duration of the period in the hospital, at times to high levels. Where rigid ward management was instituted to prevent this dissemination,<sup>6</sup> some degree of success was occasioned, and the streptococcus complications were reduced; while in wards where there was cultural evidence of the rapid contact spreading of hemolytic streptococci among patients with measles, serious complications due to these microorganisms were always encountered in the greatest numbers, appearing usually after an interval of a week or ten days from the time of onset of the contact dissemination.

The evidence indicates wide variations in the incidence of hemolytic streptococci and that the segregation of individuals, whether sick or well, is attended by a dissemination of this particular group of upper respiratory bacteria. Attending this dissemination, particularly among individuals already suffering with acute respiratory disease, there is the appearance of streptococcus complications, frequently in epidemic proportions. And yet, a comparison of the numbers of individuals acquiring hemolytic streptococci in their upper respiratory tracts under such conditions, with that of those among them who develop clinical manifestations of infection due to hemolytic streptococci,<sup>7</sup> has shown that the latter is made up of only a relatively small percentage of the former. Thus, even with widespread dissemination, hemolytic streptococci do not develop the property of inciting serious pathological processes generally among all acquiring the microorganisms.

Except under epidemic conditions, hemolytic streptococci have a rather low pathogenicity for man, so that they, of necessity, become opportunists—gaining access to foci already injured—the open wound, the postpartum uterus, the pneumonic lung, etc.,

where they gain the ascendancy and very quickly extend to mask the whole process by the seriousness of the infection set up.

When acute respiratory disease exists in epidemic proportions, and where patients are crowded together for treatment, active transfer of respiratory bacteria from individual to individual occurs. The recently traumatized respiratory tracts provide ideal fields for the transplantation and rapid development of the opportunists among the respiratory bacteria. Conditions are analogous then to the laboratory experiment for increasing virulence by rapid, successive passage through susceptible animals. In epidemics the non-immunes provide the means for this rapid transfer of infection, each in turn emitting a more deadly virus than he received. The epidemic wanes only when the non-immunes become fewer and more widely scattered, thereby decreasing the frequency of transfer. The virus persists for a time in convalescents and in the immunes gradually losing in virulence. The immunes further serve to maintain the endemic character of the virus. Epidemiological facts bear this out, in that, during the rise of the epidemic prevalence of a disease, the greatest mortality rate is recorded, while after the peak of the epidemic passes, the mortality rate declines.

**CARRIERS OF HEMOLYTIC STREPTOCOCCI.** The foregoing observations lead to a more definite consideration of the classification of individuals harboring hemolytic streptococci as recognized by throat cultures. The term "carrier" will be applied to such. Three distinct types may be defined:

1. *The Chronic Carrier.* This type of carrier is represented by a certain small number of individuals who may or may not have had acute clinical symptoms attending the acquisition of the streptococcus, but who thereafter carry small numbers of hemolytic streptococci over extended periods of time. In such cases "ragged," hypertrophied tonsils may furnish the opportunity for the organisms to continue growing more or less passively. Mild chronic inflammations may be kept up in part by such infections. Chronic carriers are likely to be distributed more generously among individuals with diseased tonsils. It is this type of carrier which maintains the endemic streptococcus manifestations. It is quite probable that from time to time there may be transient manifestations of acute infection in the chronic carrier, amounting to anything from symptoms of a "rough" throat to those of acute tonsillitis. In such cases, this carrier may, for a time, become,

2. *The Acute Carrier.* This type of carrier is represented by the individual who has active acute symptoms caused by hemolytic streptococci. Such carriers harbor larger numbers of the organisms than the chronic carriers; are more active foci of dissemination; and, presumably, have organisms of higher virulence. Throat cultures from this type of cases show very frequently almost pure

cultures of hemolytic streptococci. The acute carrier may carry the organisms for a short period during convalescence, or may carry them for longer periods, thus adding to the number of chronic carriers. It is this type of carrier which directs attention to the epidemic spreading of hemolytic streptococci. The number of these carriers is relatively small as compared with the total number of carriers which may be present in certain groups of individuals. Among patients under treatment for measles, or for respiratory diseases, a greater number of acute carriers develop than among individuals otherwise normal. Evidence has been presented<sup>7</sup> which indicates that this type of carrier develops with the initial appearance of the particular strain of hemolytic streptococcus in the throat. The number of these carriers appearing in any particular group varies directly with the widespread prevalence of,

3. *The Contact Carrier.* This class of carrier is represented by a large number of individuals who acquire hemolytic streptococci in their throats under conditions favoring aëro-contact dissemination, and who do not develop symptoms referable to the presence of such organisms. These carriers vary widely in numbers, from none at all to 75 per cent or 80 per cent of a community. The number is directly dependent upon conditions favoring the spread of infection from individual to individual. Fluctuations in the number of these carriers cause the wide variations observed in the incidence of carriers at different places and in different seasons. From this class arise the acute carriers under epidemic conditions. Members of this class appear to act as stepping stones in the building-up of virulence of hemolytic streptococci in any particular epidemic, since acute carriers begin to develop somewhat later than the beginning of the upward trend of the contact carriers.<sup>8</sup>

THEORETICAL CONSIDERATIONS IN REGARD TO CARRIERS OF HEMOLYTIC STREPTOCOCCI. The argument presented will be based upon conclusions and hypotheses suggested in this study and in the study of hemolytic streptococci in the ward treatment of measles.<sup>9</sup> The terms "acute," "chronic" and "contact" carriers will be used to apply strictly in accord with the definition of each of these as presented in this paper. A brief *résumé* of the deductions from the data collected follows:

The great variations in the prevalence of hemolytic streptococci in different communities are due to the fluctuations in the number of the contact carriers. These in turn develop under conditions favoring epidemic building and aëro-contact dissemination of the organisms.

Contact carriers spread streptococci to normal individuals, most of whom in turn become contact carriers. Contact carriers harbor the organisms for a comparatively short time. The rapid transfer of hemolytic streptococci, by means of the contact carriers, presum-

ably enhances the virulence of the strain transferred. Contact carriers after several weeks do not themselves appear to be prone to develop into acute carriers.

Acute carriers appear for the most part among individuals suffering from acute respiratory disease. These acute carriers begin to appear after there has been considerable development of contact carriers. Acute carriers develop from a recently acquired strain of hemolytic streptococcus. The strains of streptococcus harbored by the acute carriers are, perhaps, more virulent than those harbored by the other forms of carriers.

Chronic carriers serve in maintaining the endemic manifestations of hemolytic streptococci, and as such are the primary foci of dissemination in epidemic building.

Any attempt to account for the varied circumstances attending the development of these different kinds of carriers must be regarded as theoretical, and as such it should be based upon lines of reasoning following what is at present known of the nature of the organism in question. Little is known definitely of why an organism at one time produces grave infection while at another time it produces only a passive infection in the same or in different individuals.

We endeavor to explain these differences, on the one hand, by variations in virulence of the organism and by differences in the manner and in the size of the inoculation; while, on the other hand, we assume different grades of susceptibility to the infection on the part of the individuals. The former may be said to determine when the organism attacks; the latter whom it attacks. These conditions pertain especially to hemolytic streptococcus infections of the respiratory tract and their extensions.

1. *Virulence of Hemolytic Streptococci.* No one can doubt but that the streptococcus implanted upon a pneumococcus pneumonia, producing within forty-eight hours a phlegmon of the lungs and pleura with widely scattered areas of suppuration, septicemia and death, differs in virulence from the streptococcus oftentimes found in the throat of a patient throughout the course of his pneumonia. Differences in the resistance of individuals cannot account entirely for these discrepancies in the grade of the infection. Furthermore, we know definitely from animal experiment that the virulence of hemolytic streptococci vary and that virulence may be raised by frequent passage through animals.

Do the hemolytic streptococci found in throats vary in virulence? Why? In answer to these questions we need only apply the analogy between frequent passage of a strain of hemolytic streptococcus through experimental animals and its frequent transfer from individual to individual by natural means under conditions where men are crowded together. One strain may pass from *a* to *b* to *c* to *d* and so on almost indefinitely. It may grow passively in the throats of *a*, *b* and *c* and build in virulence slowly; but, sooner or later, it will reach a throat where local conditions the better

favor its growth, or the throat of an individual who has a lowered general resistance. Here it grows rapidly, produces symptoms, builds in virulence quickly, and is ready to produce sudden grave symptoms in the next individual furnishing a particularly good field for growth. These latter individuals are the acute carriers. They appear to carry organisms developed to higher grades of virulence, and are sources of immediate danger in wards treating acute respiratory diseases. These cases appear to arise because of the development of a heightened virulence in a strain of hemolytic streptococcus by its frequent transfer. In the process of this development, many individuals, such as *a*, *b* and *c*, must play a part without themselves being actually the ones to suffer. The delayed appearance of serious hemolytic streptococcus complications in a ward where numerous contact carriers have been developing, is in keeping with this argument.

The cases *a*, *b* and *c* are the contact carriers. Their range within wide limits of incidence is to be expected under this conception of epidemic building. When contact carriers begin to appear in a ward, we have the first danger signal. Serious acute streptococcus infections invariably follow.

What happens in this passage from *a* to *b* to *c*, etc., if an acute carrier, with, for example, a mild grade of tonsillitis, develops, and the opportunity for transfer of the infection is not at hand? An interruption in the building of virulence occurs. Gradually, the forces of the body defense gain the upper hand and the infection, so far as symptoms are concerned, subsides. The organisms may persist on repeated cultures, or they may disappear. In the one case we have a chronic carrier; in the other, the clearing up of an acute carrier.

What is the status of virulence of the organism in case it persists and the patient becomes a chronic carrier? Two possibilities suggest themselves: (1) The organisms may persist with sufficient growth and the maintenance of sufficient virulence to cause chronic disturbances, perhaps with occasional acute exacerbations. (2) The streptococcus may persist in a more superficial growth. It then becomes an organism growing more or less outside of the body, gradually losing in virulence and tending toward saprophytic properties. As such, it may grow even in the tonsil crypts. Growing thus indifferently, it sooner or later assumes the properties it possessed in patient *a* before any interchange with other patients occurred. There is no reason to believe that as a saprophytic organism, not again causing appreciable disturbances; it in any way loses its ability for growth in other throats on transfer to them by natural means; or that it ever loses that potential virulence which may develop into active virulence on frequent transfer. In fact, there are reasons to argue from analogy that, as it tends toward saprophytic properties it becomes less highly specialized, and requires less delicate handling to obtain growth

on transfer. The development of contact carriers would be the natural result when individuals are exposed to these chronic carriers of hemolytic streptococci of low virulence.

2. *Susceptibility of the Individual.* So far as is known, immunity to hemolytic streptococci is, in its strictest sense, relative. Immunity for a streptococcus of a given virulence may be developed, but cannot be regarded as absolute protection against a streptococcus of a higher virulence. Reinfection is common. Acute carriers, which develop a relative immunity sufficient to combat successfully the infection at its height, do not necessarily maintain such high degree of relative immunity, even though the streptococcus persists, and they become chronic carriers. A decline in the relative immunity following the decline in virulence of the organism, as it persists and tends toward saprophytic properties, might be expected. Such lowered relative immunity, while always sufficient to protect against the strain carried, might not adequately protect against a branch of the same strain, which had gone abroad, and by frequent transfer again assumed high virulence. With any organism capable of a great range of shifting virulence specific immunity can only be relative.

#### EPIDEMIC BUILDING OF CONTACT CARRIERS AND ITS CONTROL.

The data at hand is sufficient to warrant a brief discussion of the hemolytic streptococcus situation in the army camps in 1917 and 1918. We have learned to appreciate the hospital ward situation with regard to hemolytic streptococci, but have failed to appreciate another very important consideration—the camp situation. If we look back in review of the conditions in camps where hemolytic streptococci caused the most trouble, we find that the camps themselves were highly saturated with these organisms carried by men on duty in whom practically no symptoms occurred. From Camp Taylor, an 83 per cent<sup>3</sup> saturation was reported among men on duty; from Camp Custer, 70 per cent.<sup>4</sup> At Fort Sam Houston,<sup>5</sup> 35 per cent is reported among admissions for measles, which signifies a higher camp incidence. It is obvious that where such conditions existed in a camp, any measures taken within the base hospital of the camp would be, in large part, inadequate in controlling the streptococcus situation. The data cited for men from outlying country districts,<sup>2</sup> and that from Camp Taylor, for men arriving at camp,<sup>3</sup> shows that hemolytic streptococci were not prevalent among such men. The conditions where 70 to 80 per cent of men in a camp carried hemolytic streptococci must have developed in the camp, and it is not difficult to appreciate how such conditions may arise there. The one fact of fundamental importance to be appreciated in this connection is, that hemolytic streptococci may spread quite as readily among healthy men as they do among patients in a hospital. This dissemination has not been recognized because the large majority who acquired hemolytic streptococci showed no symptoms. In other words,



they were simply contact carriers. Those who developed symptoms (acute carriers) came into the hospitals perhaps for these symptoms alone, but more frequently for some other acute infectious disease, and the part which the hemolytic streptococcus played was appreciated only after it had produced serious complications. At this time, the tendency was to place the entire blame on the hospital without going back to the real place of origin.

Camp conditions favored the epidemic building of contact carriers of hemolytic streptococci for a number of reasons.

Foremost among them was the bringing together of large numbers of men, many of country origin, and the crowding of them into barracks where the conditions, if anything, were even more favorable for the spread of respiratory infections than were those of the hospital ward, because the same precautions were not taken to prevent it. This was, of course, necessary in the handling of large numbers of men, but one must face the fact and place the blame for camp epidemics of respiratory infection primarily on this circumstance. If the real dangers of this procedure are fully appreciated, there are many practical precautions that could be instituted which would tend to lessen the danger. The epidemic building of contact carriers of hemolytic streptococci in a camp should be guarded against just as assiduously as the building of an epidemic of measles, or of influenza, because of the very serious way in which the streptococcus later modifies the complications of these diseases.

Another very important factor in the rapid building of large numbers of contact carriers was the intermingling of recruits and men who had been in the camp for a time. The figures already cited for camp populations and for recruits showed vast differences in the incidence of hemolytic streptococci in the two groups. Recruits when placed in contact with men, of whom 4 out of 5 are carriers of hemolytic streptococci, would immediately be "fired" with the predominating hemolytic streptococci. Not only were hemolytic streptococci always available, but also measles and influenza have been at hand for the susceptible recruit. Multiple infection, of course, would place him at a decided disadvantage. Rapid increase in the number of contact carriers, as has been suggested, may favor the building in virulence of hemolytic streptococci and should be considered. What could have better favored the epidemic building of contact carriers within the camp than the "installment" method of bringing recruits into camp, as was done under the operation of the draft? Draft A was brought into camp, and after allowing time for the men in this group to exchange mouth bacteria, and for contact carriers to reach their height, draft B was brought in, thus adding fresh fuel to the flames and allowing the contact carriers to build to a higher plane. Other drafts followed at regular intervals before the effects of the last draft had subsided. In this manner, the most ideal conditions

were furnished for epidemic building in the camp. Recently, these conditions have been reproduced in epidemiological studies among experimental animals in the laboratory.<sup>10</sup> Records show that each of these drafts of recruits had its own quota of measles, of influenza and of pneumonia. From a knowledge of the rapid spreading of hemolytic streptococci by contact, it is only fair to assume that each had its own quota of contact carriers of hemolytic streptococci. It appears that a camp incidence of 70 to 80 per cent of contact carriers could have been built up only under such ideal conditions. The holding of the different drafts apart as entirely separate units until the throat bacteriology of the newest draft could have been interchanged and become more or less stabilized, would of itself have been a great factor in preventing such epidemic building.

A third consideration, which amounts to much the same, was the mingling of country and city recruits in the same organizations. Because of the congested conditions of city life, the throat bacteriology of urban recruits quite likely is more varied and complex than that of recruits from country districts, so that a mixing of the two groups would add impetus to the spread of mouth organisms among the recruits from the country.

**Summary.** The findings presented represent a study of acute respiratory diseases during an interepidemic period.

The pneumococcus is returning to its own in dominating the field in sporadic pneumonias.

Hemolytic streptococci and *Bacillus influenzae* are present, existing as endemic viruses at their lower planes of virulence, yet ever ready to flare up as deadly factors in the complications of epidemic pneumonia, should it return.

Three types of carriers of hemolytic streptococci are defined.

In the building of epidemics of acute respiratory disease, many individuals who themselves escape the ravages of the disease, are concerned as elementary transfer agents in the preparation of a virus (*e. g.*, hemolytic streptococci) of sufficient virulence to attack with alarming surety.

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## A ROENTGENOLOGICAL STUDY OF TUBERCULOSIS OF LUNGS AND INTRATHORACIC GLANDS IN INFANCY AND EARLY CHILDHOOD.

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THE high incidence of unsuspected tuberculosis in respiratory infections is strikingly brought home to the pediatrician conversant with an active roentgen-ray service. The routine application of roentgen-ray laboratory facilities serves to cut down the percentage of avoidable error in final diagnosis and helps materially in prognosis.

It is difficult to apply our knowledge of tuberculous changes gained through experience with adult pathology. In the infant early changes are much more massive, reactions more intense, and a definite predilection of the lymphatic structures to disease confuse exact interpretation of actual pathology. Acute serous changes predominate. Chronicity is the exception. The early stage may be of difficult differentiation and only the subsequent course enlightens us as to the true etiology. Our classification shall be a simple one as it strikes a roentgenological observer. Generally speaking, changes fall into two headings: (1) Those involving the glands; (2) those attacking the parenchyma.

1. *Glandular Changes*. These fall into three subdivisions, namely:

- (a) Paratracheal.
- (b) Perihilus.
- (c) Peribronchial.

Finer classifications can be made, but a fusion of these processes is so general that for working purposes more divisions are cumbersome.

2. *Parenchymal Changes*. These are subdivided into those involving:

- (a) Lungs.
- (b) Pleura.

**Glandular Tuberculosis.** Generally speaking, we have found that the paratracheal glands are involved earliest in life, the perihilus somewhat later and the peribronchial latest in childhood. Sometimes the process confines itself to one region, occasionally more than one. In this case one site may be heavily involved and the other or others slightly so. Eventually an entire chain is affected.

*Early Changes.* Such a plate shows in the upper mediastinal region an evenly outlined shadow, rounded or elongated, depending

upon the degree of congestive reaction and the number of glands involved. Smooth contours and unilateral shadows of even density characterize this stage. If the process is perihilus or peribronchial, the changes apply to these respective regions.

Conflicting shadows in this region are neoplasms and congenital anomalies, which are very rare, and thymus, which in contradistinction is usually bilateral, and in good plates shows a fine leaf-like arborization.

Differentiation from non-tuberculous processes at this stage is difficult and only subsequent events can clear up the diagnosis.

The second stage of changes, and that of more characteristic pathology is that due to necrosis and fibrosis. Outlines are irregular and blotchy, and so-called mottling is present. Occasionally, one may notice a zone of parenchymal congestion, and when these various changes are simultaneously present, the diagnosis of tuberculosis is probable. The ultimate outcome of these changes has been twofold; in one type, a retraction of shadow takes place, with an increase in density and an accentuation in the mottling; in the other type, a definite progression to parenchymal involvement with a picture which falls under the heading of mixed parenchymal tuberculosis.

#### **Parenchymal Tuberculosis.**

1. Pleural.
2. Pulmonary.

*Pleural Changes.* These have been of two types; an intralobar effusion, secondary as a rule to hilus gland pathology. The process is sharply defined usually between the upper and middle lobes. It subsides, as a rule, leaving a definite transverse, linear scar. However, not all linear scars are tuberculous.

The second type of pleuritis is usually found as a complication of a diffuse, pulmonary involvement, the picture of which overshadows pleuritic changes. These changes are either serous or fibrous. Serous deposition is usually in small quantities. Fibrous depositions take place in the form of fine filament-like bands or in rare instances, a diffuse, thick, plastic mass, not unlike that seen in the adult pleuritis. All combinations of these two types usually are present. At no time have we seen a primary, uncomplicated tuberculous serous or fibrinous pleurisy.

*Pulmonary Changes.* There are three types: (1) Bronchitic; (2) bronchopneumonic or lobular; and (3) lobar.

1. The bronchitic type is but a stage of pulmonary changes observed early in a general miliary infection, when the tubercle's growth is barely discernible by plate methods and when death intervenes before full growth of tubercle has taken place. At this time, markings are accentuated and somewhat congested in appearance. This type of change is also seen with general miliary

abscesses, due to a terminal sepsis. Should the disease be prolonged, the process merges into the secondary bronchopneumonic type.



FIG. 1.—An example of annular shadow in an infant with a concomitant bronchopneumonic process. Arrow points to lower border of shadow.



FIG. 2.—Diffuse terminal miliary tuberculosis grafted upon a chronic one. Terminal condition is an immense cavity with a diffuse involvement.

2. The bronchopneumonic or lobular type may be a bronchopneumonia from the very beginning, or it may be, as described

above, a stage in the bronchitic type. The lobular type may be an isolated area of involvement in any of the lobes, more often the



FIG. 3.—An example of paratracheal glands and a right sided perihilar pneumonia.



FIG. 4.—A perihilar, bronchopneumonic process of the left lower lobe; likewise a diffuse and unilateral enlargement on the right side, suggesting a universal involvement of all glands on this side.

lower, and usually perihilus in site, or there may be a general diffuse extensive involvement, no area larger than  $\frac{1}{2}$  cm. in diameter. In the first instance the parenchymal process may retrogress, the glandular condition partially subside and a period of latency vary-



FIG. 5.—An example of hilus tuberculosis with right-sided paratracheal glands.



FIG. 6.—An example of a cavity which occupies the entire right upper lobe, the terminal result in the case of tuberculous pneumonia.

ing in time may intervene, followed by a flare-up of pathology. This may be repeated and go into a characteristic tuberculous process or subside completely without any parenchymal scars. The glands, however, always bear traces. This is the recurrent

perihilus, pneumonic type, the differentiation of which is so difficult and the exact diagnosis so often overlooked.

In the cases of diffuse involvement the whole lung is so riddled that few areas of normal tissue are distinguishable. Complicating this picture, are minute effusions, fine fibrous bands, and occasionally localized areas of thickened pleura. A plate of this type shows every conceivable pulmonary change; small cavities, glands, large areas of amalgamated pathology, and occasionally small areas of spontaneous pneumothorax due to ruptured pulmonary tissue.

3. The lobar type or massive tuberculosis is probably the rarest of all types. We have had instances of not only involvement of one entire lobe right from the beginning, but we have seen an entire lung disabled, so that it was impossible to eliminate the diagnosis of effusion, so similar was the plate pathology. Only repeated negative aspirations and autopsy findings overcame our hesitant interpretation. The course of this type of pneumonia was in two directions.

In one type, a retraction of pathology to a small area and a definition of the process to only part of the lung takes place. This is an instance of the massive response of the organism where the actual area of involvement was considerably less than the early changes depicted. The process now assumed a characteristic and definite evolution to a central area of softening and a typical abscess cavity. Practically no fibrous walling off takes place, and if the condition is permitted to continue its way, the abscess breaks through and we see a localized pneumothorax. Abscess cavities may be single or multilocular, minute or the size of the better part of an entire lobe. If, however, as in the second type, the infection is overwhelming and death intervenes early in the disease, the process may end with a lobar involvement without abscess formation. This shadow is almost liver-like in its quality.

In all types the other lung may remain comparatively free without any determinable changes for a considerable time after the original process has been seen, but inevitably involvement of one type or other takes place. The guiding post in diagnosis in the early stages is the usual concomitant glandular involvement. Prognosis, of course, is bad.

*Annular Shadow.* We mention this because we have had two instances of this present in infancy; in one case with a bronchopneumonia and glandular changes suggestive of tuberculosis, and in the other, without any tuberculous pathology. There are no tuberculous stigmata, and at the last observation, it is still present. Inasmuch as the significance of this is *subjudice*, we present this evidence for what it may be worth.

We take without question the use of the roentgen-ray as an adjuvant to exact diagnosis of tuberculosis in the later years of life. Why not broaden its application to infancy and the pre-



school age? Modern medicine, with its emphasis upon *prevention* should avail itself of this assistance. Surely, there are no technical difficulties, as any patient roentgenologist can prove. If the interpretation is still groping, then only wider experience can overcome that lack.

For prognosis its value is incalculable. For assistance in exact diagnosis in infancy when clinical signs are confusing, we cannot overestimate its value, not only in tuberculosis but in respiratory infections of all kinds.

**Conclusion.** Tuberculosis in infancy is of two types, acute and chronic; the first is the more common of the two and may be subdivided into:

1. Tuberculosis of the glands.
2. Tuberculosis of the lungs.

In both cases, by means of roentgen-ray follow-up, the process can be shown to have a definite and fairly orderly sequence, a period of congestion, a period of retraction or spreading, complete or incomplete and a period of softening.

While it is true, in the early or congestive stage, the process may not be distinguishable from any of the acute infections, in the second stage, of retraction or expansion, the condition assumes characteristic appearances and in the third stage, of pathology, there should be no difficulty in diagnosis.

For exact visualization of these changes, repeated and roentgenographic investigation is absolutely essential.

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## CARCINOMA OF THE ESOPHAGUS.

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FROM August 1, 1919, to August 1, 1921, 154 patients suffering from cancer of the esophagus were studied in the Mayo Clinic.\* I have been able to trace all but 2 of these patients through the coöperation of their friends, relatives and attending physicians. A critical analysis of the group is herewith submitted.

As pointed out by Waggett, Janeway, Guttman, Held, Portis and others, malignant disease in the esophagus is much more common than is generally believed. Guttman and Held assert that from 5 to 7 per cent of all cancers found in man are in the esophagus, and Portis believes the percentage to be 20. In spite of this, reports of cases have been rather isolated, owing probably

\* Sixty-two patients having malignant lesions at the cardia involving the lower esophagus secondarily, seen during the same period, have not been included in this series.

to unsatisfactory treatment and hopeless prognosis. In 1920, Turner reported a diagnostic-statistical study of 140 cases of the disease. The majority of reports have come from those interested in some particular form of treatment.

**Symptoms.** The symptoms depend largely on the stage of the disease. In the early stages there is usually slight dysphagia when swallowing solid food, and as the lesion progresses soft foods and finally liquids become obstructed. Food obstruction is progressive with no remissions. The onset of dysphagia is usually gradual, but may be sudden. At the time the first symptom manifests itself the disease is, of course, well advanced so there is very little hope of making an early diagnosis, although in many cases it can now be made much earlier than in the past.

Hiccough is an early and not infrequent symptom. Regurgitation is common, but is usually brought on voluntarily to rid the esophagus of obstructing material; it is rarely delayed, as in cardio-spasm, and as there is usually very little dilatation of the esophagus above the stricture, the amount of food and mucus regurgitated is not large. Blood streaks in the regurgitated material are not commonly noted. Where the lesion is high in the esophagus, the constant expectoration of thick, tenacious mucus is very annoying. Because of food restriction there is continual loss of weight; the patients are rarely cachectic, yet there is a characteristic haunted facial expression. Pain may be present in the early stages, but is usually a late manifestation. It is located substernally, sometimes in the epigastrium, and may or may not accompany the act of swallowing. Occasionally hoarseness, due to cord paralysis from pressure on the recurrent laryngeal nerve from the primary growth or from metastatic cervical glands, may be the first manifestation. Hemorrhage and perforation are often terminal events. The average duration of symptoms in the series of 154 cases was seven months; the shortest duration was three weeks.

**Age of Patients.** One hundred twenty-seven of the patients were men and 27 women, a ratio of about 5 to 1. Almost all of the patients were more than forty years of age (Table I). Only 7 were less than forty, and the youngest was thirty-four years.

TABLE I—AGE INCIDENCE.

Years.	Patients.
Youngest 34 . . . . .	2
Oldest 77 . . . . .	2
31 to 40 . . . . .	7
41 to 50 . . . . .	31
51 to 60 . . . . .	61
61 to 70 . . . . .	38
71 to 80 . . . . .	17

**Location and Incidence of Lesions.** Syphilis of the esophagus rarely occurs, and it is doubtful if it was a factor in any of the cases

in this series. Eight of the patients had had syphilis, but only 4 had positive blood Wassermann reactions; the test was made in 87 cases.

Table II shows the occupation of the patient. Most of them gave histories of bolting food, meals at irregular intervals, and many used alcohol to excess. Dental sepsis was almost always present.

TABLE II—OCCUPATIONS.

Patients.		Patients.	
Farmer . . . . .	33	Engineer . . . . .	1
Home . . . . .	25	Flagman . . . . .	1
Laborer . . . . .	19	Foreman . . . . .	1
Merchant . . . . .	10	Inspector . . . . .	1
Clerk . . . . .	6	Janitor . . . . .	1
Not stated . . . . .	6	Lawyer . . . . .	1
Bookkeeper . . . . .	4	Lumberman . . . . .	1
Carpenter . . . . .	4	Machinist . . . . .	1
Miner . . . . .	4	Minister . . . . .	1
Bricklayer . . . . .	3	Nightwatchman . . . . .	1
Butcher . . . . .	3	Orderly . . . . .	1
Teamster . . . . .	3	Papermaker . . . . .	1
Baker . . . . .	2	Peddler . . . . .	1
Druggist . . . . .	2	Physician . . . . .	1
Shoemaker . . . . .	2	Plumber . . . . .	1
Architect . . . . .	1	Salesman . . . . .	1
Boilermaker . . . . .	1	Stenographer . . . . .	1
Boxmaker . . . . .	1	Tailor . . . . .	1
Builder . . . . .	1	Teacher . . . . .	1
Cabinetmaker . . . . .	1	Waiter . . . . .	1
Car repairman . . . . .	1	Writer . . . . .	1
Cook . . . . .	1		
Total . . . . .			154

The location of the lesion varied according to sex. Sixteen of the 27 women had lesions of the introitus, whereas 64 of the 127 men had lesions located from 27.5 to 37.5 cm. from the incisor teeth (Table III).

Twenty-one of the patients had metastasis; 11 were from lesions of the introitus. Nine of the patients had metastasis to the cervical glands, 1 to the lungs, and 1 to the substernal glands. Of the 10 other patients metastasis to the lungs was evident in 5, to the cervical glands in 4, and to the cervical glands and wall of the chest in 1. Seven of the patients were women and 14 were men. The apparent greater tendency for metastasis to occur in cases of lesion of the introitus is probably owing to the fact that the cervical glands were usually involved and the condition more easily recognized. As the majority of the women had lesions of the introitus, the relative increase in metastasis in this sex may be more apparent than real. Turner does not consider metastasis in his cases, but he shows very strikingly that the postcricoid cancers predominate in women. Ninety-eight of the 140 lesions reported by him were located in this area and 85 of the 98 patients were women.

TABLE III—LOCATION OF LESION.

Distance from incisor teeth, cm.			
Cm.	Cases.	Women.	Men.
18.75 . . . . .	27	14	13
20.0 . . . . .	8	..	8
21.25 . . . . .	3	1	2
23.75 . . . . .	4	..	4
25.0 . . . . .	3	1	2
26.25 . . . . .	4	..	4
27.5 . . . . .	6	..	6
28.75 . . . . .	4	..	4
30.0 . . . . .	4	3	1
31.25 . . . . .	3	..	3
32.5 . . . . .	17	4	13
33.75 . . . . .	7	..	7
35.0 . . . . .	9	..	9
36.25 . . . . .	10	..	10
37.5 . . . . .	5	..	5
38.75 . . . . .	4	..	4
40.0 . . . . .	5	..	5
41.25 . . . . .	2	..	2
42.5 . . . . .	2	..	2
43.75 . . . . .	1	..	1
45.0 . . . . .	1	..	1
Upper third . . . . .	3	1	2
Middle third . . . . .	6	..	6
Lower third . . . . .	15	3	12
Not stated . . . . .	1	..	1
Total . . . . .	154	27	127

A history of previous trauma to the esophagus was not elicited in any case, but in a recent case there had been a burn of the esophagus from lye in infancy.

One of the patients had had cardiospasm with dysphagia for nine years. He had a widely dilated esophagus with obstruction of the barium meal at the cardia (Fig. 1). Esophagoscopy examination revealed epithelioma on the anterior wall of the middle third of the esophagus.

**Diagnosis.** The diagnosis of carcinoma of the esophagus is, in most cases, relatively easy. Plummer, however, has called attention to frequent errors in diagnosis, and Miller, Hyman and Jane-way have recorded the fact that these patients may show post-mortem lesions unsuspected during life. The history is of the greatest importance in recognizing malignant esophageal disease. The cautious passage of a blunt olive on a whalebone staff guided to the obstruction by a previously swallowed silk thread is also of value and is of the utmost importance when forcible dilatation with sounds are employed in the treatment (Fig. 2). When sounds are passed through the stricture, using the wire spiral as a guide on the thread, a pink tinged mucus, sometimes foul smelling, is usually noted on the spiral when it is withdrawn; this is almost pathognomonic of cancer. Roentgenograms were made in most cases in the series, and when the obstruction was irregular in out-

line, the diagnosis could almost be made on this evidence alone. However, the roentgen examination must not be accepted as infallible; in 4 of our cases a most careful examination failed to reveal obstruction in the esophagus. Esophagoscopy examination may clear up a doubtful diagnosis but neither is this infallible. Unless ulceration is evident it is probably not wise to remove a section for microscopical examination. Not infrequently the tissue removed reveals inflammatory changes only, when there is an underlying carcinoma.



FIG. 1 (A332,370).—Cardiospasm complicated by epithelioma at the middle third of the esophagus.

Carcinoma of the esophagus must be differentiated from all other lesions producing dysphagia. However, about one-half of all esophageal lesions are due to carcinoma. Ninety per cent of patients more than forty years of age, without a history of previous trauma, who have had dysphagia for a year or less, have malignant obstruction in the esophagus. When these facts are considered, errors in diagnosis should be infrequent.

**Treatment.** The present mortality from malignant esophageal disease is practically 100 per cent, and therefore treatment should be directed along the lines of greatest palliation. Successful surgical removal of growths located at the introitus have been reported by

Turner and Wallace. Torek<sup>35</sup> has reported the successful removal of the growth in the middle third of the esophagus. Meyer, Bengölea and Lilienthal have reported resections in this location, but

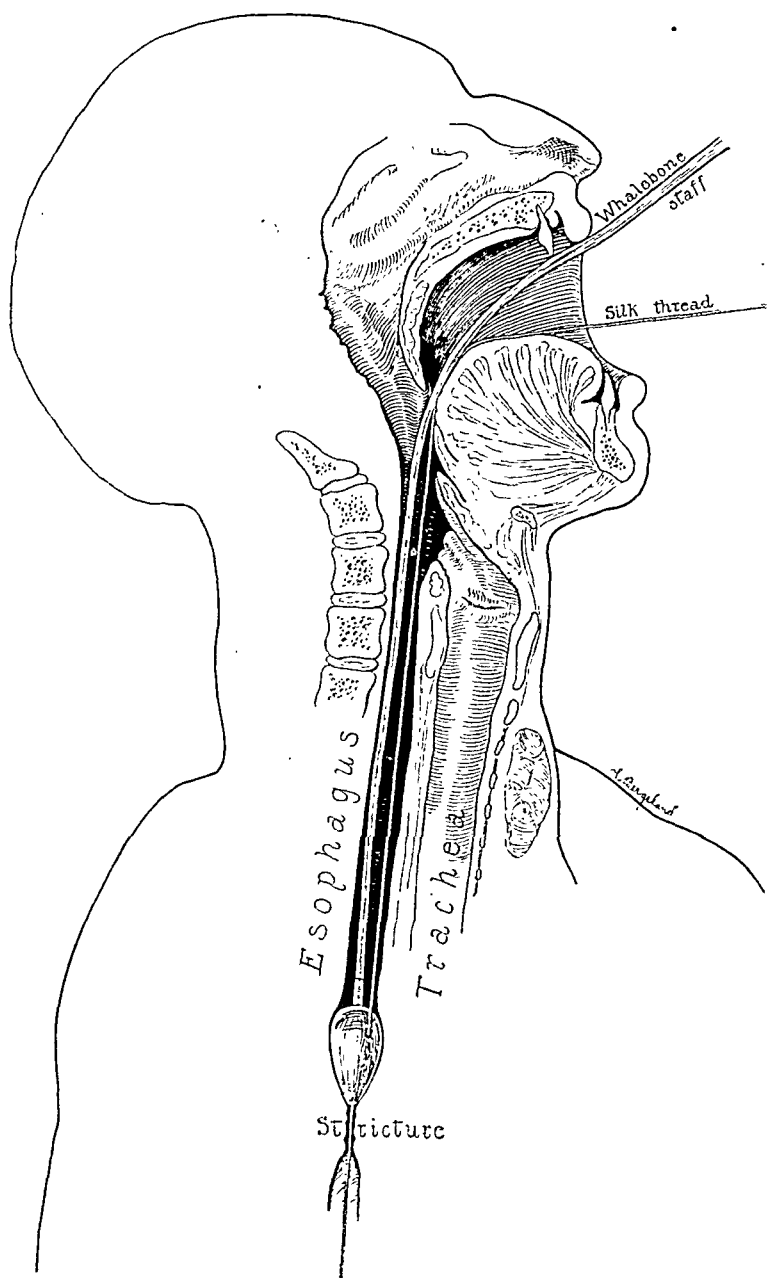


FIG. 2.—Method of measuring distance of obstruction from incisor teeth.

the benefits obtained were temporary only. Torek, in 1915, also reported resections of the lower esophagus and cardia by Völcker, Kümmell and Zaaijer. Hedblom recently reported a resection of the

lower esophagus and cardia for carcinoma. In 1917, W. J. Mayo performed a successful total gastrectomy removing 16 mm. of the esophagus.

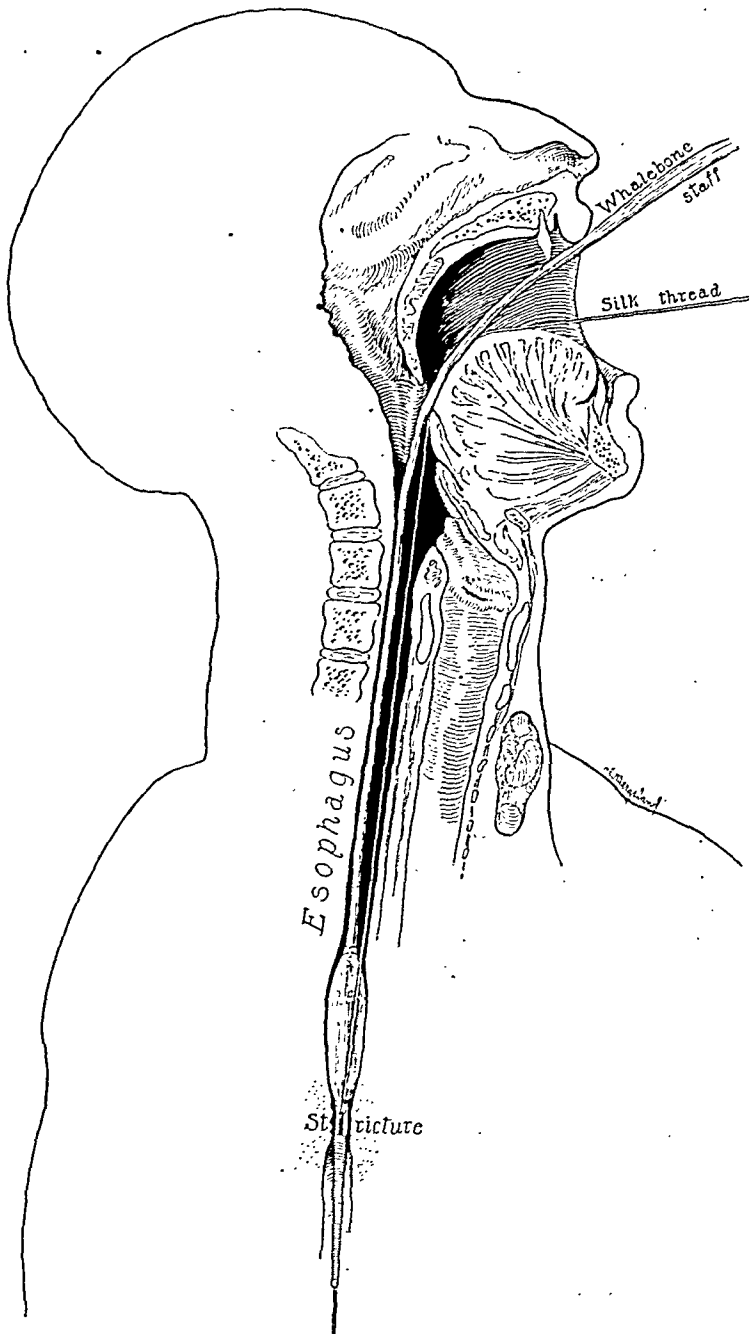


FIG. 3.—Method of dilating malignant stricture.

Surgery for the cure of these lesions is still in the experimental stage. Early diagnosis may bring about more cures, but the opera-

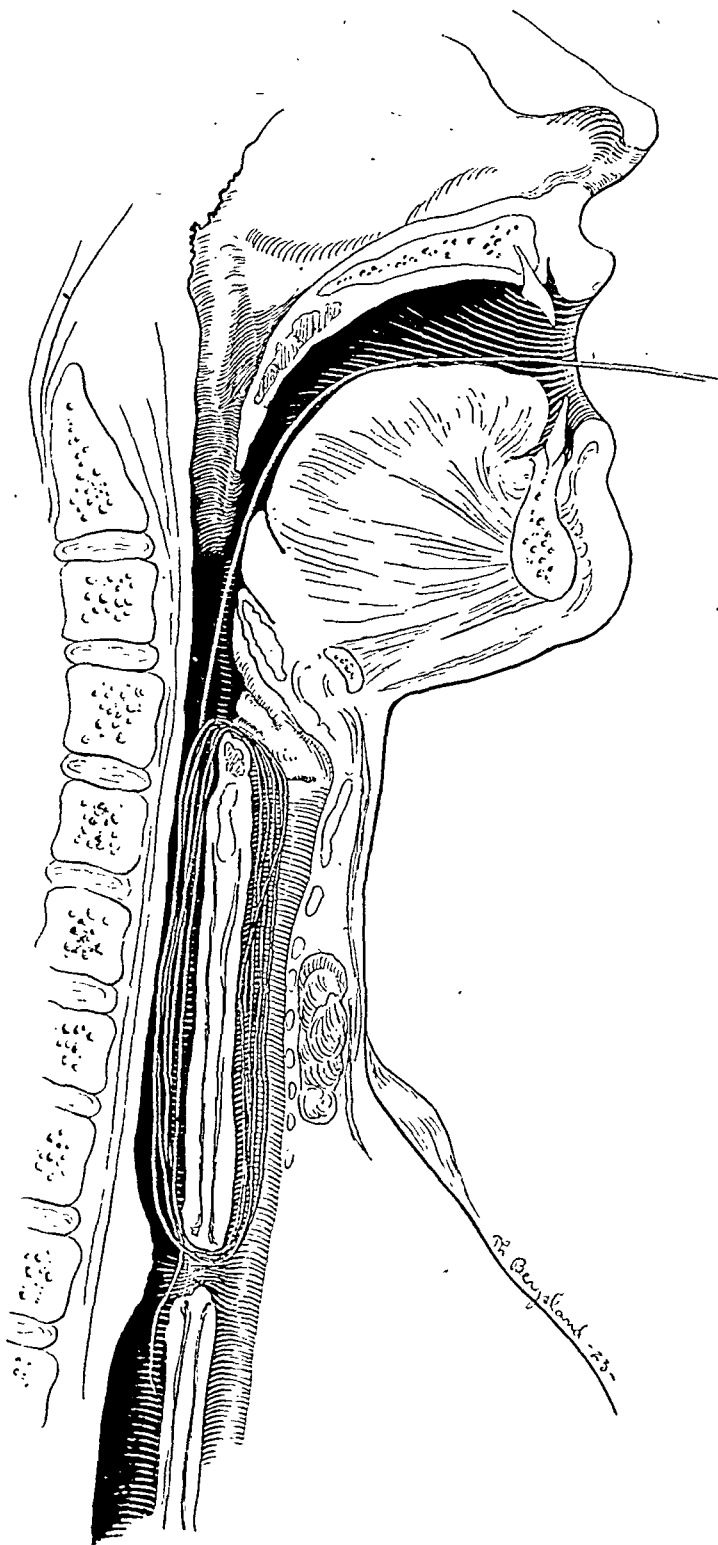


FIG. 4.—Esophago-tracheal fistula due to carcinoma. The thread is shown passing through the fistula into the trachea.



tion at best is formidable. Gastrostomy is advocated by many, particularly Jackson, Robson, Kreuscher and Lane, while Maclay decries this operation, particularly in the late stages of the disease. There are certainly just criticisms of the operation. The patients and relatives are usually very unhappy afterward, and if the disease is in an advanced stage the mortality is strikingly high. The operation really does not prolong life to any appreciable extent. Four of the patients had had this operation before coming to the clinic, and 11 had the operation at the clinic. Five of the 11 died within a week, from hemorrhage or infection; the average duration

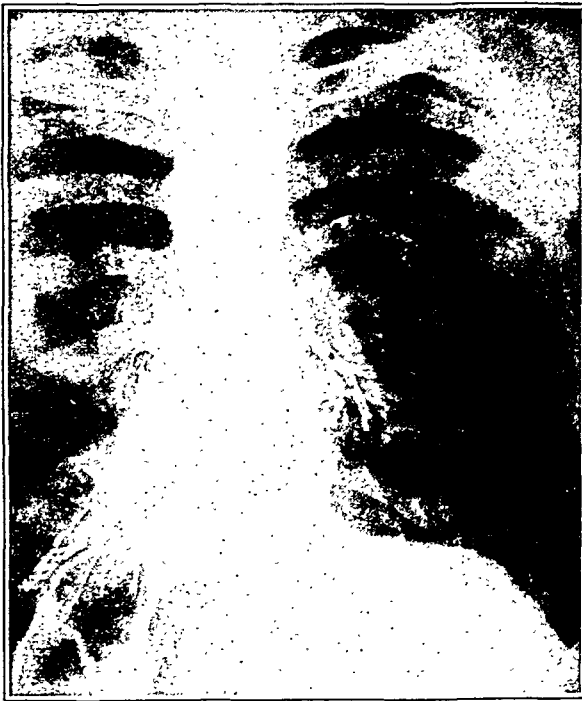


FIG. 5 (A322,470).—Esophago-tracheal fistula due to spontaneous perforation of a malignant esophageal stricture. Outline of bronchial tree is shown by the ingested barium meal.

of life after operation in the cases in the series was three months. Esophagostomy has been suggested if the lesion is high in the esophagus, but this would seem less desirable than gastrostomy.

Radium and roentgen-ray treatments have been employed extensively, but no cures have been reported although palliation has evidently been obtained in many cases. Fifteen of the patients in the clinic were treated with radium and roentgen-ray, by the technic described in a previous paper. The most favorable cases were selected for this study, but the results obtained were altogether disappointing. One of the patients lived for twenty-three months

after treatment, but the average duration of life was only eight months. The patients received from 2000 to 3000 mg. hours of radium. Recently this dosage has been increased to 3600 mg. hours without definite benefit. Intubation of the malignant stricture has been done in some instances, but not in the cases seen at the Mayo Clinic.

Although no form of treatment will prolong life for many months, or give great relief from dysphagia, it is the experience in the Clinic that the dilatation of the carcinomatous stricture with olives, graduated sizes, gives the greatest palliation (Fig. 3). Those



FIG. 6 (A391,159).—Carcinoma of the esophagus with marked distortion of the lumen of the stricture. The blind passage of sounds in such a case will likely result in perforation.

objecting to this form of treatment say that it is dangerous, that it hastens metastasis, and that it does not relieve symptoms. In 125 patients in this series the esophagus was forcibly dilated and 3 deaths resulted. Many of the patients had several dilatations. No evidence has been obtained to suggest that dilatation in any way hastens metastasis. When an esophageal carcinoma is dilated to 45 F. immediate relief from dysphagia almost always follows, and this palliation lasts for from six to eight weeks. Further dilatations will usually afford relief, but of shorter duration. The average duration of life in this series after dilatation was five months. One patient not included in the series lived for three years

following a single stretching. He finally died from generalized metastasis.

All of the dilatations were done with sounds devised by Plummer and according to his technic. A word of warning should be given in reference to the swallowing of the silk thread used as a guide in passing sounds. In cases of esophago-tracheal fistulas the thread will pass into the trachea and will be coughed up and swallowed again. In this way as many as ten or more strands of the thread may become entangled as is shown in Fig. 4. If the thread is not removed it may produce edema of the larynx, necessitating tracheotomy. Removal of the thread is a very tedious process.



FIG. 7 (A386,623).—Carcinoma of the cardia with diffuse dilatation of the esophagus resembling cardiospasm.

Eleven patients of the series were not treated and the average duration of life was three months.

**Conclusions.** 1. The incidence of carcinoma of the esophagus is higher than is generally believed.

2. The symptoms are ordinarily quite characteristic and their duration from onset to death is one year.

3. Men are much more susceptible than women, the ratio being 5 to 1.

4. Carcinoma of the esophagus is rare in persons under forty years.

5. In men the lesions are most common in the middle third of the esophagus, whereas in women the growths predominate in the upper third.

6. Demonstrable metastasis is infrequent but occurs more often with lesions of the introitus and, therefore, is proportionately more common in women.

7. Previous trauma to the esophagus is not a definite factor in the causation of malignant esophageal disease.

8. The history of the case, and the cautious passage of sounds, are the most valuable factors in making a correct diagnosis.

9. The roentgenogram is of value in making a diagnosis, but is not infallible.

10. The esophagoscope is of limited value in diagnosis and treatment.

11. The mortality in untreated cases is 100 per cent, and surgery offers very little as a curative or palliative measure.

12. Radium or roentgen-ray therapy is practically valueless.

13. Forcible dilatation of the malignant stricture gives greater relief than any other form of treatment.

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## INTESTINAL INDIGESTION IN ECZEMA AND PSORIASIS.\*

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(From the Skin Clinic and read before the Staff of the Massachusetts General Hospital.)

**I. Foreword.** "Man, who is the servant and interpreter of Nature, can act and understand no farther than he has, either in operation or in contemplation, observed of the method and order of Nature. The knowledge and power of man are coincident; for whilst ignorant of the cause he can produce no effects; nor is Nature to be conquered but by submission. And that which in speculation stands for the cause is what in practice stands for the rule." Bacon.<sup>1</sup>

**II. Intestinal Indigestion.** In this period of advanced civilization in which complex conceptions and ultra-scientific theories are sometimes elaborated, man is after all—what he has been and always will be—merely a servant and interpreter of Nature. He is the most highly perfected animal, yet like all lower forms is subject to the natural laws already made known and interpreted. These laws are just, but exacting and economical in operation; and are expressed in the animal economy, or the nice adaptation of the parts or organs of living creatures to the service they perform. There are many examples of economy in man; but the nice adaptation of the alimentary tract to the processes of digestion and absorption in proper nourishment is undoubtedly the most essential consideration in the maintenance of a harmonious and healthy body.

Some phase of the animal economy is evidently brought into action by the dietary treatment of intestinal indigestion; for by reducing the quantity and improving the quality of the alimentary mixtures in many patients with eczema and psoriasis, a better action of the gut appears to be elicited, the amount and kind of nourishment is improved, and the patient becomes healthier. In general the treatment consists of educating the patients to refine and proportion the food properly and when these requirements have been fulfilled for a sufficient length of time, the condition of the skin improves. But this improvement is also accompanied by a change in the intestinal rate and the consistency of the feces. The intestinal rate becomes slower and the feces firmer, thus indicating an increased amount of absorption. With the change in the consistency, there is likewise a change in the form of the feces. At the beginning of treatment the dejections are soft and formless as shown in Fig. 1; later they become formed with marks and similar to Fig. 2; and finally when all of the functions of the

\* This investigation was made possible through a Lowell Fund.

gut appear to be in action, they are formed in units with marks, as shown in Fig. 3. Accordingly as the alimentary mixture improves it is made subservient to bodily action, is controlled by the intestinal rate and the form of the feces, and is better suited to the animal economy.

In the first place, it may seem peculiar that there is an improvement in an unhealthy skin with a slowing of the intestinal rate, as this process is supposed to have a detrimental effect on the body. Under these circumstances however, it is necessary to be critical; and while a slowing of some mixtures may be harmful, it is not so with all. Then again, estimates of the intestinal rate have not



FIG. 1



FIG. 2



FIG. 3

FIG. 1.—The soft and formless feces.

FIG. 2.—A stool formed with marks.

FIG. 3.—The feces entirely formed in units.

been made accurately; they have generally been made from symptoms rather than by ingesting a substance and observing the number of hours it takes to pass completely through the gastrointestinal tract. And if the intestinal contents elicit one of the normal intestinal functions—antiperistalsis—there is a reversed passage of the contents in the proximal colon, which undoubtedly makes the rate slower. In the second place, stools entirely composed of discrete masses or fecal units are generally supposed to be a sign of constipation. In practice this is also an erroneous supposition; for when the aliment passes along the canal regularly at about the same slow rate, two dejections are common daily instead of one. Furthermore, as most mammals normally deject

dung entirely in discrete masses, it is impossible to conceive that all of these animals are constipated.

These conceptions are perhaps due to an ignorance of the normal intestinal rate, to an unwarranted fear of the effects of a slowing of the intestinal rate in all cases; but more particularly to a lack of knowledge of the delicacy and complexity of the normal intestinal functions in completing the cycle of digestion and absorption. These intricate processes may be explained by a consideration of the three most essential forms of intestinal motility, as shown in Fig. 4. In the first process or rhythmic segmentation an elongated mass is seen in the ileum at A, but as it passes along it is suddenly divided by a series of constricting rings into small ovoid segments shown at B, then by a second series of constrictions each segment

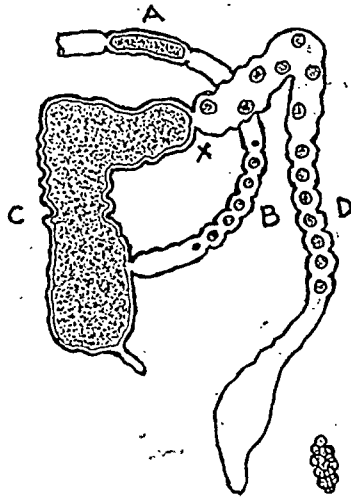


FIG. 4.—A diagram of the human gut, showing the three most essential forms of intestinal motility: (1) Rhythmic segmentation in the ileum at A and B; (2) peristalsis and antiperistalsis in the proximal colon at C; and (3) haustral churning in the distal colon at D. X represents the physiological constricting rings that limit the proximal colon.

will be halved, and half of number one will join with half of number two, the other half of two will join with half of number three, and so on. These segments will once more be halved and reunited. Such a division and reunion of the intestinal contents may continue for some time; and it is by this process that most of the absorption from the intestinal contents takes place. Afterward the remaining chyme is passed into the first portion of the large intestine or the proximal colon (C). Here it joins with the material already in the sac, and, being retained by the physiological constricting rings at X, is kneaded back and forth by waves of peristalsis and antiperistalsis in the second form of intestinal motility. Later the soft pultaceous material is divided again into discrete masses in the intermediate colon, and propelled along the distal colon. In



this part of the gut they are still further acted on in the final process or haustral churning at D. This action is somewhat similar to rhythmic segmentation, excepting that in this final moulding of the intestinal contents the masses remain discrete and are dejected in fecal units.<sup>2 3 4</sup> Such a distribution of the intestinal contents in man is shown in Fig. 5. While these complex forms of intestinal motility represent only the mechanical functions, "we may expect to find that the rate of passage through the different parts of the tube is nicely adapted to the speed of the chemical changes."<sup>5</sup> Accordingly, with mechanical actions and chemical changes complete, the intestinal contents must supply complete nourishment.



FIG. 5.—A roentgen-ray picture of the human colon taken twenty-five hours after a barium meal. The large shadow on the left is an outline of the proximal colon, while the distal colon is filled with fecal units. The distribution of the intestinal contents is similar to the preceding diagram.

The amount and kind of food ingested by man has been considered from many points of view, but it seems incredible to realize that these sensitive and complex functions of the gut are undoubtedly forces in the body having a selective action on the quantity and quality of the alimentary mixture; and in the requirements of the body for nourishment are far more accurate than the wisest conceptions. In other words, by selective action, mixtures that are properly refined and proportioned will complete the cycle of digestion and absorption; but those that are coarse, badly balanced or incomplete, will be passed along rapidly and cause indigestion and malnutrition. A process of this kind, whereby a

mechanical function is brought into action by a chemical stimulant is beautifully illustrated by the acid control of the pylorus. There is, however, more direct experimental evidence to support such a contention. For instance, Cannon has found that rhythmic segmentation was readily observable in cats following the action of a protein mixture, whereas a fat or carbohydrate mixture seldom elicited this complex function.<sup>6</sup> And Magnus found antiperistalsis present in cats with a suitable mixture, but when senna was added to the mixture this function was not elicited.<sup>7</sup> Then Erlanger and Hewlett observed that if dogs having most of the small intestine resected, were given proper food, they had formed feces and maintained their weight; but by adding a certain amount of fat to the food, diarrhea was produced and the animals rapidly became emaciated.<sup>8</sup> Finally McCarrison, by experimenting with monkeys fed on a deficient and ill-balanced diet, has found the functions of digestion, absorption and assimilation to be the first to fail, and are shown by loss of appetite, vomiting, and diarrhea.<sup>9</sup> From these observations it is evident that the gut has a selective action on the alimentary mixtures and passes along rapidly those that are not suitable for nourishment; but mixtures that are refined, well-proportioned and complete elicit the proper functions of the gut, are properly reduced chemically and the individual receives the nourishment in amount and kind that should be obtained from the food.

In a previous communication on "Fecal Units and Intestinal Rate, a Basis for the Study of Health and Intestinal Indigestion," the form of the feces has been presented to determine two exact conditions of the body.<sup>10</sup> The basis for such a hypothesis is readily understood from an examination of the specimens illustrated in Figs. 1 and 3. The former is a soft and formless mass, whereas the latter is entirely composed of units and discrete masses having a smooth surface which is broken here and there by irregular lines. These units and lines must be the result of some of the intestinal functions; but the soft and formless feces show a loss of some of these functions. It is generally considered that a loss of one of the vital functions is an indication of disease. Therefore the soft and formless stool affords a very definite means of determining a heretofore unrecognized disease—intestinal indigestion. On the other hand, the feces entirely composed of units are similar in form to the normal dung of animals. And when some of these animals are given deficient or unsuitable food, the dung often changes to a pasty and formless condition.<sup>11</sup> In the second place, the unit form of the feces conforms to the physiology of the gut as previously described. In the third place the requirements necessary to produce this form by man are exacting and when not fulfilled the stool changes to a soft and formless condition. In the fourth place, the

continued dejection of fecal units by an individual or race\* is associated with an improved physical condition. And finally, patients whose feces have been changed from a soft and formless condition to one entirely composed of units, by a course of dietary treatment alone, have improved in health and been relieved of some very resistant conditions of disease. Therefore it is difficult not to say that the unit form of the feces is normal, and affords a very definite and immutable means of determining a heretofore unrecognized condition of the body—an improved state of well being.

If the rate at which the intestinal contents pass through the alimentary canal is nicely adapted to the speed of the chemical changes, a loss of function in one portion of the gut results in a corresponding incomplete chemical solution and insufficient or improper nourishment. Such a loss of function has been found to be due to a chemical agent, such as the ingestion of too much rich food. On the other hand the proper preparation of the food for digestion by thorough comminution and mixing with the saliva, is essential to produce the unit form of the feces. Accordingly when the food is bolted there seems to be another kind of action. This is probably bacterial in origin, and results in an excessive or peculiar putrefaction of the intestinal contents. An observation by Beaumont is quite in accord with this assertion. "Mastication is absolutely necessary to a healthy digestion. If aliment in large masses be introduced into the stomach, though the gastric juice will act on its surface, chymification will proceed so slowly that other changes will be likely to commence in its substance before it will be completely dissolved."<sup>12</sup> It is evident therefore that two factors are in operation in producing intestinal indigestion; one is chemical and the other a bacterial agent. Malnutrition is associated with both, but a toxemia resulting from an excessive or peculiar putrefaction of the intestinal contents is only due to bacterial action.

From experimental investigations carried on in animals, malnutrition has proved to be a factor in producing many conditions of disease. Thus McCarrison in a very comprehensive study of

\* Dr. McCarrison says "For some nine years of my professional life my duties lay in a remote part of the Himalayas, where several isolated races are located far removed from the refinements of civilization. Certain of these races are of magnificent physique, preserving late in life the character of youth; they are unusually fertile, and long lived, and endowed with nervous systems of notable stability. During my association with these peoples I never saw a case of asthenic dyspepsia, of gastric or duodenal ulcer, or appendicitis, of mucous colitis or of cancer. Indeed their buoyant abdominal health has since my return to the West, provided a remarkable contrast with the dyspeptic and colonic lamentations of our highly civilized communities." R. McCarrison—*Faulty Food in Relation to Gastro-intestinal Disorder*, Jour. Am. Med. Assn., 1922, 78, No. 1.

"I regret to say that I have not made observations on the form of the feces of the Himalayan tribe to which I referred; except in a most general way; but I have a distinct memory that such stools of healthy men as I have seen among these people had distinctly the unit form of health to which you refer" R. McCarrison—personal communication.

deficiency disease in pigeons, guinea-pigs and monkeys, has found that loss of appetite, vomiting, diarrhea and dysentery to be the first as well as the most pronounced symptoms and signs in these improperly fed animals. But other conditions as anemia, loss of weight, low body temperature, cardiovascular depression, asthenia, loss of hair and eczema, disturbances of the endocrine glands, headaches and symptoms referable to malnutrition of the nervous system were also produced.<sup>13</sup> By other investigators defective and irregularly formed teeth, scurvy, rickets, ophthalmia and neuritis have been produced experimentally in animals. One of these investigators has also alluded to the disorder of the gastrointestinal tract with a diarrhea or "pasty feces" as the earliest and most important sign indicating a disturbance of the body.<sup>14</sup> The process by which one of these conditions is brought about is explained in an interesting English report.<sup>15</sup> "The young animals are able to grow when the fat-soluble factor is deficient in their diet, by the assumption that the animal organism normally contains reserve supplies of this factor in its own body. If this hypothesis is correct it is reasonable to assume that these reserves are mobilized for use when a deficiency occurs in the diet, but as soon as they are exhausted growth is immediately inhibited. During the period of temporary growth. . . there does not appear to be any decline in their health, but when the reserves are exhausted and the deficiency becomes felt, not only do they cease to grow but they become highly susceptible to bacterial infection. In rats this lowered resistance first becomes apparent in many cases by the appearance of a characteristic infection of the external eye, which has been provisionally classified as a xerophthalmia."

With the results of these experimentally produced conditions of disease of animals in mind, it is interesting to make a speculative survey of the human body generally dejecting the feces entirely in units, or on a unit basis and in an improved state of well being, and compare it to one with malnutrition produced by intestinal indigestion. It would seem as if properly nourished individuals acquire a certain reserve in the body, which is manifested by a strong constitution or increased degree of vital resistance. Under these circumstances if there is an acute attack of intestinal indigestion and a temporary loss of nourishment the reserve is drawn on and the tissues of the body are unaffected. But when intestinal indigestion has continued for a long time, the reserve is exhausted and the body is bankrupt; and then under the strain of continued malnutrition the weak tissue or tissues give way and some form of deficiency disease or lowered vital resistance is produced. In this study, while the skin showed the most pronounced lesions, other conditions of disease were associated with them. For instance most of the patients gave a history of dyspepsia, some were anemic, a few had asthma, and a few had arthritis. It is evident therefore

that there is one way and only one way to combat these deficiency diseases, and that is by improving the quantity and quality of nourishment to be derived from the food. With this subtle and heretofore unrecognized factor—malnutrition as a cause of some of the deficiency diseases—the treatment of eczema and psoriasis is put in a new light. But better yet, if it is possible to control the diet of children early enough, get them and keep them on a unit basis and in an improved state of well being, and then eczema, psoriasis and perhaps other conditions of disease will be prevented.

**III. Eczema and Psoriasis.** The conditions of disease considered due to a metabolic disorder are numerous; so that with a heretofore unrecognized means for the relief of intestinal disturbances, any of them might have been worked over in a preliminary study. Eczema and psoriasis have been thought to belong to this class; and lately McCarrison has been able to produce loss of hair, a rough and scaly skin, and in some cases eczema, by feeding monkeys on deficient diets.<sup>16</sup> Then again as they have such definite objective signs, changes in the condition of the skin are readily correlated with the form of the feces. On account of these facts these abnormal conditions afforded very good material for an initial study of intestinal indigestion as a factor in the production of disease.

In general, eczema and psoriasis have been very resistant forms of disease to treat successfully. They are often alleviated by a course of treatment, but are likely to recur. They are sometimes cured, but seldom by the same external application or dietary directions. Every now and then one is cured spontaneously or without the use of any form of treatment. But as the amount and kind of nourishment absorbed by the body undoubtedly fluctuates, and yet is in operation constantly, it is impossible to ascribe a cure to a simple remedy without taking this heretofore unrecognized factor into consideration. A history of a psoriatic illustrating some of these points is interesting to describe. The case is one of a young American, who when graduating from college noticed a few red areas on the forehead near the margin of the hair. In a few years the lesions of the scalp gradually increased in size, and similar lesions appeared on the arms and thighs. At this time he consulted an eminent dermatologist in this country, was told he had psoriasis, and was advised to use an ointment. The treatment was carried out faithfully for several months; but during this time the old lesions not only got worse, but new ones appeared. The following winter he went to Vienna, and consulted the leading skin specialist. Another kind of ointment was recommended. After the salve had been rubbed into the skin for several weeks, the lesions got paler and in a few months had disappeared entirely. The patient was very much impressed by the treatment, and procured some of the ointment to use in case the lesions

reappeared. After returning to America in about a year, new spots appeared on his body. He applied the ointment, but this time it had no effect. Thinking that it might have deteriorated he had a new lot compounded; but this too did not influence the lesions. Finally believing that the new lot might not have been properly compounded, he sent to Vienna for a fresh supply; and after using this faithfully for some time without seeing a change in the condition of his skin, he became disgusted and did nothing. Within a year, however, after he had given up all form of treatment, he noticed the red patches were becoming paler. Soon afterward many of them had disappeared, and in a few more months his skin was quite clear, and has remained so for twenty years. The course of this case and its ultimate cure is interesting, yet while one kind of treatment was used at one time, another kind at another time, and finally no treatment, the amount and kind of nourishment are the most likely factors continually in operation that could have brought about an improvement, and finally affected a cure.

The history of a case of eczema likewise expresses the influence of diet on the condition of the skin. It is one of an American boy of ten, who had had the disease since infancy. He had had many different kinds of treatment in the Out-patient Department and Skin Ward of the Hospital. At times the lesions improved somewhat; but he was unable to attend school regularly, and was generally handicapped. After using external applications and dietary treatment for intestinal indigestion, he got better and went home. In a letter from his mother the following account is given of the course of his condition. "After following the directions about diet, I found a great improvement in Buddy's skin. He felt better and went to school regularly. But on the day I was to bring him to the Hospital, I got pneumonia and of course all Bud's diet and regularity went smash. When I got well I found that his face was all broken out again, and his ears, neck and chest were red and swollen. I asked him what he had been eating; and he said apples, oranges, peanuts and candy. I put him on his diet again, also used some salve, and he is getting along finely now. Before this attack, I had just got him so that his feces were formed in units as you said they should be. It is my candid opinion that your course of treatment has done more for him than anything else, and I intend to carry it out to the best of my ability." The influence of the character of the alimentary mixture and the kind of nourishment in this case is evident; for when it was refined and wholesome the boy got on a unit basis and the skin improved; but when the diet was unrestricted, intestinal indigestion and malnutrition resulted, and these factors again produced lesions of the skin.

In this study, all of the diagnoses were made by Dr. Charles J. White, Dr. Harvey P. Towle, or other members of the Dermatological

Staff of the Massachusetts General Hospital.\* In the beginning, an attempt was made to relieve intestinal indigestion in all patients with eczema and psoriasis admitted to the ward; but as the form of treatment is largely educational and some of the patients had such a low grade of intelligence, while others had so little knowledge of the English language, they were unable to understand the requirements necessary to get on a unit basis, and carry out the measures for a long period of time. Accordingly most of the patients were selected, and only those thought capable of effecting a successful outcome were worked over. The length of time the patients had had lesions of the skin varied considerably. One woman had eczema for thirty-one years; another had psoriasis for twenty-three years. The duration of most of the disturbances ranged from five to fifteen years; although there were a few cases of only a few months' standing. The forms of treatment previously tried on these chronic invalids are too numerous to review in detail. Most of them had used many kinds of salves, washes and powders, a few had tried the roentgen-ray and quartz light; some had taken arsenic, benzyl-benzoate, quinine and other drugs internally; and a few had been restricted by low protein, fat-free, and a diet according to skin reactions. Some of these measures seemed to afford relief at times. Several of the patients, however, obtained the most permanent relief by a change of environment and mode of living; for instance one psoriatic was free of lesions for a few months after spending a summer in Maine camp, and a patient with eczema likewise had a clear skin after a summer at the seashore under the supervision of a trained nurse. In obtaining a history of the habits of these patients, dietary errors were always very evident. Most of them were in the habit of eating too fast; some were continually eating between meals; a large number admitted that they ate too much sweet stuff; others spoke of taking a lot of fruit; and finally not a few had been using some form of laxative for years to relieve constipation. Those observing the feces had noticed that they were always soft. One or several of these habits were responsible for the crude or badly balanced alimentary mixture that failed to complete its cycle of digestion and absorption, and as a result of malnutrition kept the skin in an abnormal condition.

The treatment of patients with intestinal indigestion generally requires a great deal of therapeutic effort. Some having an instinctive feeling that dietary errors are responsible for the condition of the skin, understand the measures necessary to take and carry them out resolutely. They usually show an improvement in the condition of the skin after a while. Others comprehend the treatment in part or do not have the will to carry it out for a long time.

\* I wish to acknowledge the kindness and coöperation the members of the Dermatological Staff have shown me in carrying out this investigation.

They are likely to improve some time. A few get well, lose control of themselves, and have another attack. And a few do not understand at all or do not consider the form of treatment sufficiently reasonable to make an effort. They continue the same or get worse. In planning a course of treatment therefore, it is not only necessary to take the disposition into account, but also the bodily condition and the action of the gastro-intestinal tract of each patient. Then again, during the course of treatment, slight alterations have to be made from time to time in the diet according to the action of the gut. That is to say, when the feces are well formed, fruit may be added to the food, but if it causes a rapidity of the rate no more should be taken for some time. The amount of food allowed of course varies with the size and occupation of the patient, but it is generally less than had been previously consumed, for it is a matter of quality rather than quantity that has to be taken into account. In this way too, a consideration of the number of calories ingested may be misleading, as it is the alimentary mixtures that complete the cycle of digestion and absorption, instead of the amount of food put into the stomach that is the principal consideration. Again the kinds of food may not be very restricted, and consist of those that are simple, wholesome, complete and suitable for the nourishment of an omnivorous animal. Candy, jam, preserves, pickles, salad dressings, ham, pork, bacon, or rich or highly spiced food should be given up for some time; cereals and soft foods should be restricted; fresh or cooked fruit should not be eaten until the intestinal rate becomes slow. Such general information while accurate may not convey an understanding of the subject; therefore a list of about the foods often suggested for a day may be helpful. Breakfast: 1 egg, 2 slices of toast and butter, 1 cup of coffee. Luncheon: 1 lamb chop, 1 portion of spaghetti and tomato, 1 piece of squash pie. Dinner: 1 slice of roast beef, 1 potato, portion of spinach, 1 roll and butter, 1 portion of rice custard. These foods amount to about 100 gm. of protein, 100 gm. of fat, and 200 gm. of carbohydrate and the accessory substances; and taken in a light breakfast and luncheon but a good dinner. The proportion should be about the same every day as a marked change is likely to affect the intestinal motility. The time of eating should be restricted to two or three meals during the twenty-four hours; and only water should be taken between meals. On a two-meal regime a little more food may be added to the breakfast given previously and eaten in the middle of the morning, and somewhat similar dinner should be allowed in the evening. This basis is valuable for obese patients and those that have had an abnormal condition of the skin for many years. All of the food must be thoroughly comminuted and mixed with the saliva. An attempt should be made to have a movement half an hour or so after breakfast and again before going to bed. In the early part



of treatment defecation is usually successful at one of these times, but if the intestinal rate is to become slower, a day is likely to pass without a defecation. If two days pass an enema or suppository should be resorted to. Later in treatment when the feces are well formed in marks or units, two defecations are common daily. When the patient is having regular defecations, estimates of the intestinal rate are of value every week or so. For this purpose a measure of 50 cc of French millet seed in half a tumbler of water is swallowed directly after an evening meal. In the beginning of treatment when the patient has soft and formless feces, the seeds are invariably seen in the defecation the next morning, and are frequently seen for two more days; or to put the test in terms of the intestinal rate, if the seed were taken Monday at 7 P.M. and were first seen on Tuesday at 9 A.M. the initial rate is fourteen hours, and then if they are seen again on Wednesday and last seen on Thursday at 9 A.M. the final rate is sixty-two hours. Later, however, when the patient is generally on a unit basis, seeds taken Monday night at 7 P.M. are not seen until Thursday at 9 A.M. or with an initial rate of sixty-two hours, and appear on Friday and Saturday, and are last seen on Sunday at 9 A.M. a final rate of one hundred and thirty-four hours. Muscular exercise is a valuable adjunct in carrying out the treatment. And by having the patient keep a record for a week every now and then of the food ingested, the time taken for the meals, the form of the feces, and finally a test of the intestinal rate, the alimentary mixtures are better controlled. A change in the intestinal rate and the form of the feces should be brought about by this form of treatment. The change may take place in months rather than weeks. But if a change is not brought about in a reasonable time, something is wrong with the alimentary mixture and further adjustment is necessary.

For two years, while this investigation has been carried on, an attempt has been made to relieve intestinal indigestion in 30 patients with eczema and 30 with psoriasis. A few of each group having kindly consented to serve as controls have had dietary treatment only and are well; but a majority of the patients have also had external washes and ointments. The results obtained with eczema are shown in Table I.

TABLE I.—RESULTS OBTAINED WITH ECZEMA.

No. cases.	Treatment carried out.	Form of feces.	Bodily condition.
10	Generally	In units	Well.
4	Generally	Not known	Well.
6	Sometimes	With marks	Improved.
1	Sometimes	Not known	Improved.
4	Not at all	Soft and formless	Eczema.
3	Not at all	Not known	Eczema.
2	Not heard from		

The results obtained with psoriasis are shown in Table II.

TABLE II.—RESULTS OBTAINED WITH PSORIASIS.

No. cases.	Treatment carried out.	Form of feces.	Bodily condition.
15	Generally	In units	Well.
8	Sometimes	With marks	Improved.
1	Sometimes	Not known	Improved.
4	Not at all	Soft and formless	Psoriasis.
2	Not heard from		

A glance at the results obtained in the treatment of eczema and psoriasis shows that they are dependent on the amount and kind of nourishment obtained from the food. For the patients that generally carried out the treatment got on a unit basis, and after a while have been relieved of an unhealthy skin by getting into an improved state of well being. Those that have sometimes or in part taken up the treatment, have been partially relieved of intestinal indigestion and are better. While those that have not taken up the treatment at all continue to have intestinal indigestion, malnutrition, and eczema and psoriasis. Unlike other forms, the treatment is always available for those continuing to have intestinal indigestion; and several patients have made two and even three attempts to get into an improved state of well being. A few of the patients with eczema and asthma or psoriasis and arthritis have made an improvement in both conditions of disease; but the number of cases is not sufficient to be very significant. All of the patients with constipation found, after improving the alimentary mixture and getting a slower intestinal rate, that laxatives were unnecessary, as they had one and sometimes two movements a day. The weight of many of the spare patients has increased; whereas those that were obese have lost weight. And without exception all of the patients generally on a unit basis have felt in an improved state of well being.

At this time let us stop for a moment and reflect. Think of the waste of nourishment! Think of the waste of the tissues! Think of the years and years of misery that have fallen to the lot of many of these patients! And yet there are children at the present time, who will undoubtedly follow the same course. Should we not attempt to prevent such extravagance and suffering? From studying the action of the gut of a few children, it is not a difficult matter to control the food, so that they are generally on a unit basis. In Fig. 6 is shown the feces of an infant at eleven months entirely composed of units. For three years now, this child has been generally dejecting this form of the feces, and will continue to be kept in an improved state of well being as long as the diet is carefully supervised. Other children can be maintained in the same healthy condition, and in this way the needless waste of

nourishment, the needless waste of the tissues, the needless misery, and the wholly unnecessary conditions of disease—eczema and psoriasis—will be prevented.



FIG. 6.—Feces of an infant, aged eleven months, entirely composed of units.

**Conclusion.** It is evident that when the alimentary mixture is properly refined and proportioned it is made subservient to bodily action, is controlled by the intestinal rate and the form of the feces, and is better suited to the animal economy. In this way the form of the feces affords a means of determining two heretofore unrecognized conditions of the body. One, intestinal indigestion as shown by the soft and formless stool, is associated with a disorder of metabolism and malnutrition, and may be the cause of various secondary conditions of disease. It is undoubtedly a factor in the production of eczema and psoriasis; for they have been entirely or partially relieved when the nourishment of the body has been improved; and have returned again with intestinal indigestion and malnutrition. The other, an improved state of well being, determined by the unit form of the feces, is a condition in which the aliment completes its cycle of digestion and absorption, and the individual evidently receives the nourishment in amount and kind that should be obtained from the food. At this time there are many children with intestinal indigestion soon to be crippled with some bodily disorder by this form of malnutrition. With this heretofore unrecognized factor in the production of disease, we should attempt to apply this hygienic form of treatment in the relief of intestinal indigestion as early as possible, to prevent eczema and psoriasis and perhaps other conditions of disease, and to maintain the body in a harmonious and healthy state.

**IV. Illustrative Cases—Eczema.** CASE I.—P. W. O'N., a school boy, aged sixteen years, has had eczema since infancy. Twice

during this period the skin has shown a marked improvement. He was in the ward of the hospital ten years ago for several weeks. Ointments, washes, internal remedies and various diets have been tried. Up to two years ago he used to eat fast, between meals, and a lot of candy and sweet stuff, and lately has been eating a good deal of fruit. Movements have been regular daily, but have always been soft.

The entire surface of the body is covered with lesions, but the skin of the forehead burns and smarts and is especially aggravating. The palms of the hands are much thickened, and some of the fingers are cracked. Feces soft and formless.

November 6, 1920. Put on a diet about as follows:

*Breakfast:* Egg, 2 pieces of toast, cup of coffee.

*Dinner:* Slice of beef, potato, portion of beets, slice of bread and butter, portion of ice cream.

*Supper:* Bowl of lamb stew with vegetables, 2 pieces of bread and butter, 2 molasses cookies.

November 10, 1920. Feces more formed.

November 23, 1920. Movements formless again; too much sweet stuff.

November 27, 1920. Skin improving. Initial rate twenty hours.

February 19, 1921. Skin better. Feces formed with marks and units.

April 30, 1921. Is now generally on a unit basis.

June 23, 1921. Skin shows a little improvement. Rate forty-seven hours.

October 11, 1921. Continues on unit basis; rate forty-eight to eighty-six hours.

March 30, 1922. Has jaundice.

May 2, 1922. Skin improving slowly. Face not so rough. Thick areas on palms smaller. Generally on a unit basis. Rate sixty-two to one hundred and forty-seven hours.

July 10, 1922. Skin continues to improve. Rate fifty to ninety-eight hours.

At present he is eating about as follows:

*Breakfast:* Scrambled egg and bacon, saucer of oatmeal and milk, cup of coffee.

*Lunch:* Slice of beef, potato, portion of stewed tomatoes, 2 slices of bread and butter, portion of rice pudding.

*Dinner:* Portion of chicken pie with potato and vegetables, 2 rolls and butter, cup of tea, glass of milk, portion of apple sauce, 2 pieces of cake.

CASE II.—H. L., an English Jew, aged forty-five years, and employed recently as an automobile-top maker, he has had eczema for thirteen years. The condition of the skin has been called

psoriasis, but is now a dermatitis exfoliativa. At times there was a little improvement, but he has never been entirely free of lesions. For nine weeks has had an acute attack. As a child had a few

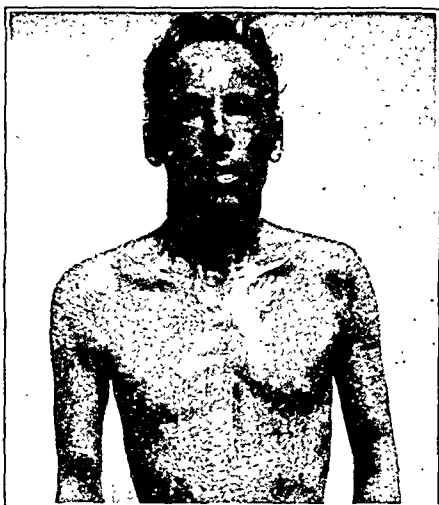


FIG. 7



FIG. 9



FIG. 8

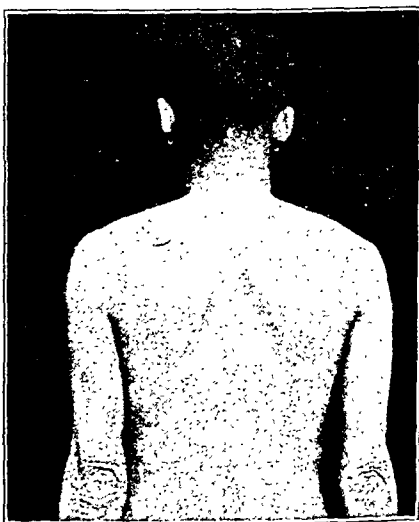


FIG. 10

FIG. 7.—Chest of H. L., with dermatitis exfoliativa.

FIG. 8.—Back of H. L., with dermatitis exfoliativa.

FIG. 9.—Chest of H. L., after four months of dietary treatment; only a little salve was used at first.

FIG. 10.—Back of H. L., after four months' dietary treatment.

attacks of eczema. Had "rheumatism" fifteen years ago; other wise general health has been good.

Always ate rapidly; spending less than five minutes at a meal, but not between meals. Used to eat a good deal of sweet stuff.

Bowels moved daily as a general rule; but sometimes had diarrhea accompanied with abdominal pain, nausea and gas. Movements are soft.

Entire body red and cracked, and covered with scales, see Figs. 7 and 8.

June 19, 1922. Given directions about diet.

June 24, 1922. Has been eating slower, spending about twenty minutes at a meal. Feces continue formless.

July 1, 1922. Feces often contain a few units.

July 8, 1922. Skin improving a little. Has been entirely on a unit basis this week. Intestinal rate seventy-four to one hundred and forty-one hours.

July 11, 1922. Went home.

October 6, 1922. Seen in Out-patient Department. Only a few lesions remain on hands and arms, as shown in Figs. 9 and 10, otherwise skin is perfectly clear. A remarkable growth of hair has appeared on the forehead. Does not have any pain in stomach, nausea or gas. Feces have been entirely formed in units since leaving the hospital.

CASE III.—A. L., a Jewess, aged fourteen years, has had eczema since infancy. At times the condition of the skin improved; supposedly according to some of the external applications and other treatments she has tried. She has been in the ward of the hospital twice, and has been coming to the Out-patient Department for treatment off and on for six to seven years.

Always ate rapidly and a lot of food; also ate between meals and a good deal of candy and fruit. Usually had a movement of the bowels regularly in the early afternoon.

April 13, 1921. At this time most of her body is covered with lesions. The patient was given dietary directions for the treatment of intestinal indigestion, and salves.

April 14, 1921. Feces are soft and formless.

April 15, 1921. No movement.

April 17, 1921. Feces contain a few units. Skin improving.

April 20, 1921. Feces are soft and formless, and due to too much fruit.

April 26, 1921. Initial intestinal rate is fifteen hours.

May 7, 1921. Skin continues to improve.

June 11, 1921. Has been entirely on unit basis for last few weeks. Skin almost clear of lesions.

July 23, 1921. The skin is now quite clear. Cautioned about eating too much fruit.

November 19, 1921. Skin is very dry. Feces have been soft and formless lately from eating too much fruit.

January 10, 1922. Has scabies and is given local treatment.

May 13, 1922. Continues on unit basis, and the skin is clear,

CASE IV.—F. L., Jewish widow, aged sixty years, has had eczema for thirty-one years. During this time she has been in the ward of the hospital seven or eight times for a few months; and has been coming to the Out-patient Department almost every week. Has tried washes, salves, arsenic, diets, Alpine lamps and roentgen-ray.

Used to eat rapidly and between meals, and also a good deal of fruit. Has been taking physic for constipation for many years. Face, hands and arms covered with red, raised itching lesions.

January 22, 1921. Given directions about diet, and put on two meals.

January 29, 1921. Bowels have been a little irregular.

February 5, 1921. Has two soft and formless movements a day without physic. Is eating too much fruit.

February 26, 1921. Skin improving a little.

March 12, 1921. Feces often formed in units.

April 23, 1921. Skin shows a decided improvement.

July 27, 1921. Is regularly on a unit basis. Skin clear. Given advice about returning to three meals daily.

September 19, 1921. Face and hands broken out with a few red patches, and there is a question of epidermophytosis. Ate something that disagreed with her and had diarrhea for a week. Permanganate put on hands, but nothing on face. Put back on two meals.

September 24, 1921. Has been back on unit basis this week; face clear and hands are better.

January 26, 1922. Skin continues clear and feels well. Still has only two meals; but generally two movements entirely in units.

CASE V.—M. C. S., a school girl, aged sixteen years, has had eczema and asthma since infancy. During this time she has been in the ward of the hospital thirteen times for three to four months at a time; and while at home had been coming to the Out-patient Department every week. All kinds of ointments and washes had been used. She had also tried fat-free and low-protein diets; and in skin tests had been found sensitive to milk, eggs, and to horse hair. One summer at seashore under the supervision of a trained nurse she got well; but lesions returned after a month at home.

Always ate rapidly, between meals, and a lot of candy and sweet stuff. Mother says her food did her no good. Stools always soft and moved two or three times a day. At this time, neck, arms and legs were covered with lesions.

August 23, 1920. The patient was told to eat only at meal times, to eat slowly, and avoid candy, rich food, and fresh and cooked fruit for the present.

September 3, 1920. Feces formed in units.

September 11, 1920. Stools soft and formless and contain large uncomminuted lumps. Eating too fast. Is applying vaseline externally.

October 30, 1920. Has been on unit basis for some time. Skin improving.

February 19, 1921. Skin continues to improve. Is regularly on unit basis and having two movements a day.

March 1, 1921. Is in the medical ward with pneumonia. Skin worse.

April 16, 1921. Skin no better. Movements continue soft and formless. Has been eating too much fruit.

July 28, 1921. Has generally been on a unit basis for sometime. Skin of neck and face normal; and hands and legs are better. Asthma also improved.

September 19, 1921. Skin continues to improve. Intestinal rate thirty-eight to one hundred and forty-five hours.

**Illustrative Cases—Psoriasis.** CASE VI.—F. J. R., an American pharmacist, aged thirty-three years, had had psoriasis for eight years. The second summer it almost disappeared. Being a pharmacist he has tried a great many internal and external remedies, but did not find one that brought an improvement in his skin.

Always ate moderately fast, and a good deal of candy and peanuts between meals. Liked fruit and ate a lot of it. Has been constipated for years and has had to take a laxative almost every night. Stools always soft and formless.

Was told to eat about as follows:

*Breakfast:* A portion of creamed beef, 2 slices of toast, cup of coffee.

*Dinner:* Portion of lamb, potato, portion of cabbage, slice of bread and butter, portion of tapioca pudding.

*Supper:* Bowl of beef soup, portion of macaroni, slice of bread and butter, piece of cake, cup of cocoa.

April 4, 1922. Movements have been irregular.

April 8, 1922. Feces sometimes formed with marks. Rate twenty-seven to one hundred and eighteen hours.

April 15, 1922. Skin improving. Movements are sometimes in units. Rate fifty to one hundred and twenty-three hours.

April 22, 1922. Generally has two movements a day entirely in units.

May 15, 1922. Since returning home has been eating too fast and too much. Had indigestion and did not feel well. A few new spots appeared on his skin. Feces often soft, with a rate of twenty-seven to eighty-six hours.

July 5, 1922. Skin improving.

July 10, 1922. Lesions have disappeared. Regularly on a unit basis and generally having two movements a day. Rate sixty-two to one hundred and thirty-six hours.

At present is eating about as follows:

*Breakfast:* Two pieces of toast, glass of milk, cup of coffee.



*Dinner:* Piece of boiled pork, potato, portion of cauliflower, slice of bread and butter, piece of apple pie, glass of milk.

*Supper:* Portion of cheese, potato, slice of bread and butter, portion of custard, glass of milk, cup of tea.

CASE VII.—J. F. C., an American laborer has had psoriasis for six months. Always ate a great deal, between meals and fast; also ate a large amount of fruit, but candy and rich food in moderation. Sometimes had diarrhea but usually had a large soft movement in the afternoon. Seldom took physic. On the advice of local doctor has been eating less and eating slower.

On examination the entire body is moderately covered with ringed raised red and scaly lesions, see Fig. 11. Feces partly formed in units, with an intestinal rate of twenty-four hours.

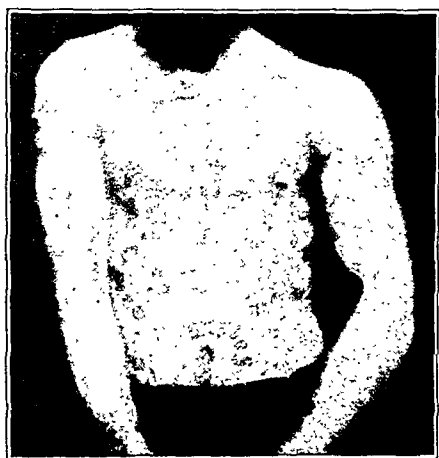


FIG. 11

FIG. 11.—Chest of J. F. C., with psoriasis.



FIG. 12

FIG. 12.—Chest of J. F. C., after three months of dietary treatment.

The patient was given ordinary house diet, but without fresh or cooked fruit, ham or bacon, and cereals. He is also using ointment.

July 6, 1921. Has had movements daily, and some of them have been formed entirely in units. Intestinal rate seventy-two to ninety-six hours.

July 12, 1921. Allowed a banana.

July 13, 1921. Feces soft and formless.

July 14, 1921. No movement.

July 15, 1921. On unit basis again.

August 13, 1921. Continues on unit basis. Skin shows a decided improvement.

August 20, 1921. Ate a banana without changing form of feces.

October 3, 1921. Skin about clear (see Fig. 12) and he eats about what he likes. Still on unit basis. Rate sixty-four hours.

December 4, 1921. Has been eating too much fruit. Feces often soft and formless. A few new lesions have appeared on chest.

January 1, 1922. A lot of new lesions have appeared. Got back to his former habits again; and has been eating too fast and too much, between meals and a good deal of fruit and sweet stuff. Feces continue soft and formless. Intestinal rate seventeen to forty-two hours. Given dietary directions.

January 29, 1922. Is back on unit basis again. Rate forty-three to one hundred and fifteen hours.

February 12, 1922. Lesions becoming a lighter color. Regularly on a unit basis. Rate forty-four to one hundred and thirteen hours.

March 27, 1922. Continues on unit basis. Rate forty-five to ninety-six hours.

April 30, 1922. Large clear areas in center of most lesions. Rate sixty-four to one hundred and thirty-nine hours.

June 3, 1922. Skin almost clear. Has not used external applications during this attack. Rate fifty to one hundred and twenty-eight hours.

August 20, 1922. The skin is now quite clear. Is generally on a unit basis. Rate sixty-two to one hundred and thirty-four hours.

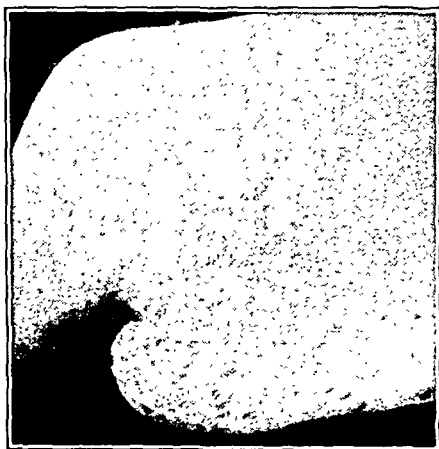


FIG. 13

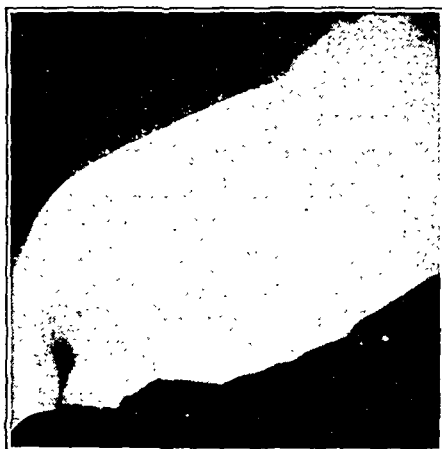


FIG. 14

FIG. 13.—Shoulder of J. A. McL. with psoriasis.

FIG. 14.—Shoulder of J. A. McL. after a year of dietary treatment. This patient kindly consented to serve as a control, and did nothing but improve her nutrition.

CASE VIII.—J. A. McL., an American housewife, is moderately fat. She has had psoriasis for twenty years in patches generally covering the body; and in spite of trying various external applications and internal remedies, it has remained about the same. Has not had asthma or rheumatism.

Always ate rapidly and a large amount of food. Did not eat

between meals. Generally ate a good deal of sweet stuff, but was moderate with fruit. Took a good deal of medicine at one time. Used to have a movement of the bowels regularly on arising.

The body is generally covered with small red, raised and scaling lesions, which are larger and more numerous on lower extremities. See Fig. 13.

July 16, 1920. Given dietary directions but is not to use external or internal remedies.

July 23, 1920. Movements irregular. Has had several after breakfast that were soft and formless.

August 6, 1920. No new spots have appeared.

August 18, 1920. Intestinal rate twelve to thirty-three hours.

September 3, 1920. Feces sometimes contain a few units and generally has a movement every day. Rate twenty-four to X (not observed) hours.

September 8, 1920. Rate forty-nine to one hundred and eight hours.

September 24, 1920. Spots becoming paler. Rate fifteen to one hundred and two hours.

February 5, 1922. Letter. "Skin shows remarkable improvement. In splendid health. Movements regular and often in units. Initial rate seventy-two hours. Has lost 10 pounds."

February 27, 1922. Skin about clear. See Fig. 14.

CASE IX.—W. A., an American school boy, aged twelve years, has had psoriasis for seven years. Several times in the summer the lesions disappeared, but they returned again in winter. Has tried many ointments and salves.

Eats a large amount; is especially fond of potatoes, and eats a large number daily. Has always eaten fast, and a good deal of candy and fruit between meals. Usually has a single soft movement after breakfast.

Entire body covered with red raised scaly lesions. (See Fig. 15.) Feces soft and formless. Allowed house diet—without fruit and cereals. Used ointment.

April 5, 1921. Feces formed with marks, rate twenty-seven hours.

April 21, 1921. Has some difficulty in eating slowly. Feces soft and formless. Rate seventeen hours.

September 1, 1921. Letter. "Skin has improved a little. Stools all right and sometimes three a day. Is eating slower, but a good deal of fruit and candy."

March 17, 1922. Came to the Out-patient Department. Skin again covered with lesions. Got into bad habits once more and has been eating too much, too fast, and too much fruit and candy. Given dietary directions and ointment.

March 20, 1922. Rate fourteen to sixty-two hours.

March 25, 1922. Rate twenty-eight to ninety-six hours.

April 4, 1922. Most of the lesions have disappeared, is eating less and slowly; and no candy, little fruit. Is generally on a unit basis. Rate forty to one hundred and thirty-four hours.

October 6, 1922. Skin is clear (see Fig. 16). Is generally on a unit basis. Initial rate forty-eight hours. Has gained 3 pounds.



FIG. 15

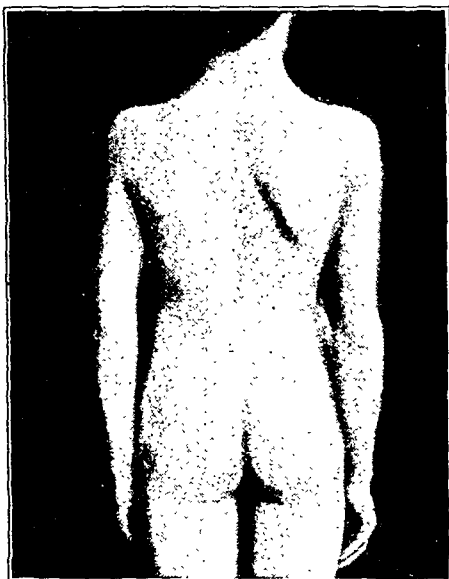


FIG. 16

FIG. 15.—Back and thighs of W. A., with psoriasis.

FIG. 16.—Back and thighs of W. A., five months after generally carrying out dietary treatment.

CASE X.—O. J. B., an American housewife, is very fat, and has had psoriasis for five years. Two years ago during pregnancy it almost disappeared. Has tried all kind of external applications and diets.

Always ate fast, between meals and a lot of candy and sweet stuff. Fruit in moderation. Bowels moved any time but frequently had to use suppositories. Surface of body slightly covered with small red scaling lesions.

September 29, 1921. Given dietary directions.

October 13, 1921. No new spots have appeared. Movements more regular and better formed. Rate twelve to one hundred and eight hours.

October 20, 1921. Rate twenty-four to one hundred and thirty hours.

October 28, 1921. Rate ten to one hundred and fifty-six hours.

November 2, 1921. Rate twenty-six to one hundred and eight hours.

December 13, 1921. Skin much better. Has not used any ointment for six weeks. Movements often formed with marks. Rate nineteen to one hundred and thirty-four hours.

January 1, 1922. Rate twenty-two to one hundred and seven hours.

February 3, 1922. Skin about well. Only a few spots remain. Feces mostly in marks, but has seen a few units.

April 1, 1922. Rate twenty to one hundred and thirty-five hours. Is pregnant. Has lost about 30 pounds.

## SUMMARY OF CASES—ECZEMA.

No. case.	Age.	Duration of disease in years.	Time observed in months.	Treatment carried out.	Form of feces.	Bodily condition.
1 F. B.	9	7	12	Sometimes	Not known	Improved.
2 J. M. B.	49	3	12	Not at all	Not known	Eczema.
3 I. M. B.	50	5	6	Not at all	Formless	Eczema.
4 W. J. B.	56	20	12	Generally	Marks	Improved.
5 B. D. B.	17	5	12	At times	Formless	Eczema.
6 A. D.	18	$\frac{3}{4}$	10	Sometimes	Not known	Well.
7 M. D.	23	$\frac{1}{2}$	1	Generally	Marks	Well.
8 J. C. F.	67	1	4	Generally	Marks	Well.
9 C. M. G.	73	20	15	Generally	Units and marks	Well.
10 E. C. G.	16	2	12	Not at all	Formless	Eczema.
11 J. A. H.	48	20	6	Generally	Not known	Well.
12 D. J. H.	23	$\frac{1}{4}$	6	Generally	Units and marks	Well.
13 F. T. J.	4	3	1	Not heard from		
14 M. K.	52	3	8	Not at all	Not known	Eczema.
15 R. K.	35	7	12	Not at all	Not known	Eczema.
16 H. L.*	45	13	5	Generally	Units	Well.
(Case 1)						
17 F. L.*	60	31	20	Generally	Units	Well.
(Case 2)						
18 A. L.*	14	8	18	Generally	Units	Well.
(Case 3)						
19 J. M. M.	60	5	8	Generally	Marks and units	Improved.
20 M. H. M.	63	1	15	Generally	Units and marks	Well.
21 M. F. M.	14	1	6	Generally	Not known	Well.
22 L. F. M.	33	30	6	Generally	Units and marks	Improved.
23 A. M.	14	5	8	Generally	Units and marks	Well.
24 P. W. O'N.*	15	15	24	Generally	Units and marks	Improved.
(Case 4)						
25 S. A. P.	22	20	1	Not heard from		
26 W. R.*	10	9	18	Generally	Units, marks and formless	Well, two attacks.
(Case 5)						
27 H. A. R.	72	4	24	Generally	Units and marks	Improved.
28 M. S.	16	15	24	Generally	Units and marks	Improved.
29 M. V. S.	13	12	2	Not at all	Not known	Eczema.
30 E. W.	4	2	8	Generally	Units and marks	Well.

\* Given more in detail under illustrative cases.

## SUMMARY OF CASES—PSORIASIS.

No. case.	Age.	Duration of disease in years.	Time observed in months.	Treatment carried out.	Form of feces.	Bodily condition.
1 W. A.* (Case 6)	12	7	20	Carefully of late	Units and marks	Well.
2 C. A.	58	20	3	Generally	Units and marks	Improved.
3 O. J. B.* (Case 7)	24	5	12	Generally	Marks	Well.
4 E. F. B.	38	8	14	Sometimes	Marks	Improved.
5 R. E. C.	10	1	6	At times	Units, marks soft and formless	Got well had second attack.
6 A. Mc	24	3	1	Not heard from		
7 C. L. C.	15	6	25	Generally	Units and marks	Well.
8 J. F. C.* (Case 8)	25	$\frac{1}{4}$	25	Generally	Units, marks soft and formless	Well, two attacks.
9 L. M. C.	42	23	24	Sometimes	Marks and soft and formless	Improved got worse
10 E. J. F.	32	14	12	Not at all	Soft and formless	No better.
11 A. F.	41	12	18	Not at all	Soft and formless	Worse.
12 M. T. H.	38	15	22	At times	Marks	Improved.
13 E. G. H.	35	$\frac{1}{4}$	6	Generally	Units	Well.
14 C. J. H.	24	10	24	Now and then	Marks	Improved.
15 B. J.	22	3	6	Generally	Marks	Almost well.
16 E. C. J.	26	8	25	Sometimes	Marks	Improved.
17 J. F. K.	48	6	3	Generally	Marks	Improved.
18 F. R. K.	33	15	20	Now and then	Soft and formless	The same.
19 J. A. McL.* (Case 9)	37	20	8	Generally	Units	Well.
20 C. M.	21	9	24	Sometimes	Units, soft and formless	Well two attacks.
21 A. C. M.	50	20	4	Generally	Marks	Improved.
22 E. C. N.	16	10	20	Sometimes	Units, soft and formless	Well two attacks.
23 E. P. O.	47	1	1	Not heard from		
24 B. P.	16	4	8	Generally	Units, marks	Well.
25 L. C. P.	33	1	4	Sometimes	Not known	Improved.
26 F. J. R.* (Case 10)	33	7	8	Generally	Units	Well.
27 M. F. S.	19	9	6	Generally	Units	Well.
28 G. R. T.	18	6	25	Generally	Units	Well.
29 H. I. T.	33	16	10	Generally	Units and formless	Well two attacks.
30 M. A. W.	40	10	4	Generally	Units	Well.

\* Given more in detail under illustrative cases.

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## REVIEWS.

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NUTRITION AND CLINICAL DIETETICS. By HERBERT S. CARTER, M.A., M.D., Assistant Clinical Professor of Medicine, Columbia University, New York; Consulting Physician to the Presbyterian Hospital, Lincoln Hospital, Skin and Cancer Hospital, New York; PAUL E. HOWE, M.A., PH.D., Associate, Rockefeller Institute for Medical Research; formerly Assistant Professor of Biological Chemistry, Columbia University, New York; Officer-in-Charge of Laboratory of Nutrition, Army Medical School, Washington, D. C.; and HOWARD H. MASON, A.B., M.D., Associate in Diseases of Children, Columbia University, New York; Visiting Physician, Children's Service, Presbyterian Hospital, New York. Third edition. Pp. 731. Philadelphia and New York: Lea & Febiger, 1923.

To one who has used the previous editions of this work, the appearance of a third edition is most welcome. The previous editions have proved extremely practical and of great value and with the enlargements and changes, such as appear in this newer edition, the book should prove even more practical and more useful. The authors have, in addition to thoroughly revising the book, rewritten the chapter on vitamins and the chapter on food requirements of children. The chapter on rickets has also been rewritten. They have also discussed fully von Pirquet's method of feeding and have added most valuable discussion on the importance of ketone-antiketone properties of foods in relation to diabetic diets. With these additions, the subject of dietetics may be said to be presented to the medical world in a manner which leaves but little to be desired. A practical work-a-day book on dietetics is particularly important on account of the tendency of many physicians to neglect this most important branch of therapeutics except in a few diseases, such as diabetes, in which the diet is of prime importance.

M.

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COLLECTED PAPERS OF THE MAYO CLINIC. VOL. XIV, 1922. Pp. 1394; 488 illustrations. Philadelphia: W. B. Saunders Company, 1923.

EACH year the contributions to medical literature from the Mayo Clinic seem to grow in number so rapidly that if the present plan



of compiling these contributions yearly is continued, in succeeding years undoubtedly it will be necessary to publish them as a two-volume work. The present volume contains over thirteen hundred pages and is so large as to be almost unwieldy. Aside from this criticism nothing unfavorable can be said about the work. It is well edited and well printed. The papers that go to make up the volume will be of interest to the physician interested in any phase of medicine. The report of operations, operative procedures, results of operations, etc., are, of course, in the majority, but there are a large number of medical papers as well as those devoted to the more special branches. The catholicity of the contents may be appreciated from the fact that practically every portion of the body is covered and such diverse subjects as morphea, Meniere's disease, ketogenesis, brain tumors, water intoxication and other unusual conditions are dealt with. The breadth of the contents may be judged from the fact that in the section on the alimentary tract, for example, twenty-eight articles appear. It hardly seems just to offer a review such as this but one becomes accustomed, in considering the Mayo Clinic, to deal with quantity rather than quality, and although this review has dealt almost entirely with the quantity element of the volume, it is to be stated that the quality of the presentations compares most favorably with that emanating from any other clinic or institution in this country.

M.

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NOSOGRAPHY IN MODERN INTERNAL MEDICINE. By KNUD FABER, M.D., Professor of Internal Medicine, University of Copenhagen. Pp. 222; 21 illustrations. New York: Paul B. Hoeber, Inc., 1923.

It has been truthfully said that no physician is qualified to excel in his profession unless he has a broad knowledge of the history of medicine. The internist has never had a volume devoted entirely to the history of his branch of medicine until the appearance of this present volume by Faber. Although the title of the book is *Nosography*, nevertheless the title, to a certain extent, belies the true character of the work, as it is really a somewhat sketchy but extremely interesting history of internal medicine. The author takes for his theme the idea that the clinician cannot properly functionate without the ability to label every disorder and to place it within some morbid category. With this as a basis for his work he proceeds to tell us when and how various diseases with which we are now acquainted were first described as well as how other modern, present-time procedures in diagnosis have been developed. The book is a most delightful one; and certainly, as Dr. Cole has said in his introduction, the clinicians in this country are especially fortunate that Professor Faber has been willing to translate this book into the English for our benefit.

M.

RECOVERY RECORD FOR USE IN TUBERCULOSIS. By GERALD B. WEBB, M.D., Consulting Physician, Cragmor, Glockner and Sunnyrest Sanatoria; and CHARLES T. RYDER, M.D., Cragmor and Glockner Sanatoria. Pp. 78; 108 illustrations. New York: Paul B. Hoeber, Inc., 1923.

IN this delightful presentation of a rather uninteresting subject, the authors have laid down rules for the care of the tuberculous individual who is on the high road to recovery, which the patient himself should read and learn. The last half of the volume is composed of special charts which the patient keeps to show the physician on his rounds. Above and below each chart is an aphorism from some well-known author which adds interest to the work and gives knowledge to the patient. The admirable features of this book are extremely valuable both for the patient and the physician. M.

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MEDICAL AXIOMS, APHORISMS AND CLINICAL MEMORANDA. By J. A. LINDSAY, M.A., M.D., F.R.C.P., Professor of Medicine in the Queen's University of Belfast; Consulting Physician to the Royal Victoria Hospital, Belfast, and to the Ulster Eye, Ear and Throat Hospital. Pp. 192. New York: Paul B. Hoeber, Inc., 1923.

THE axioms and aphorisms that the author presents to us are the fruit of many years of study of medical cases. They are good practical points which the average doctor would do well to tuck away in the corner of his brain for use when various contingencies arise in his practice. M.

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INDUSTRIAL HYGIENE AND MEDICINE. By E. W. HOPE, O.B.E., M.D., D.Sc., Medical Officer of Health for the City and Port of Liverpool; Professor in Public Health, University of Liverpool. In collaboration with W. HANNA, M.A., M.D., D.P.H., and C. O. STALLYBRASS, M.D., D.P.H., Assistant Medical Officers of Health for the City and Port of Liverpool, and Lecturers in Public Health Subjects, etc., University of Liverpool. Pp. 766; 123 illustrations. New York: William Wood & Co., 1923.

THIS book brings up to date, in brief and convenient form, the important facts in our knowledge of occupational health hazards, their effects and the methods of overcoming them. While somewhat less pretentious and comprehensive, it presents in the main the subject from the British point of view as did Kober and

Hanson's "Diseases of Occupation and Vocational Hygiene" from the American standpoint. It has an advantage over the latter in that includes much valuable data that has become available since the termination of the war. It is well written, fairly well illustrated and will be of distinct value to all those, medical and others, interested in the subject of industrial hygiene. M.

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VOLUME JUBILAIRE (PUBLIÉ À L'OCCASION DU CENTENAIRE DE LA SOCIÉTÉ). SOCIÉTÉ ROYALE DES SCIENCES MÉDICALES ET NATURELLES DE BRUXELLES. Pp. 766; numerous illustrations. Bruxelles: Lamertin, 1922.

THIS stately volume bears strong witness to the flourishing condition of Belgian medical and natural sciences. Following an eighty-page history of the society are more than fifty scientific articles, among whose authors are Stienon, Wybauw, Bordet, Dépage and Zunz. The format of the book is excellent and the illustrations especially noteworthy. K.

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THE DEBT OF MEDICINE TO THE FINE ARTS. By J. A. NIXON, C.M.G., M.D. (CANTAB), F.R.C.P., Physician to the Bristol Royal Infirmary; Consulting Physician to Southmead Infirmary. Pp. 29; 11 illustrations. Bristol: J. W. Arrowsmith, Ltd., 1923.

THIS essay is a most interesting contribution to the correlation of medicine with the fine arts. It is nicely illustrated and well presented. M.

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MEDICAL STATE BOARD QUESTIONS AND ANSWERS. By R. MAX GOEPP, M.D., Professor of Clinical Medicine at the Philadelphia Polyclinic; Assistant Professor of Clinical Medicine, Jefferson Medical College. Fifth edition. Pp. 731. Philadelphia and London: W. B. Saunders Company, 1923.

THOROUGH revision, with an equal number of additions and omissions, has brought this edition up-to-date, without adding to its size. It will doubtless continue to be as valuable to the candidate for licensure as it has in the past. Though the answers are necessarily condensed and often incomplete, the wide range and full index make it a useful, handy book, even for some of those who have weathered that rocky point. K.

LEGAL MEDICINE AND TOXICOLOGY. Edited by FREDERICK PETERSON, M.D., LL.D., formerly Professor of Psychiatry, Columbia University; Consulting Alienist to Bellevue Hospital, New York; WALTER S. HAINES, A.M., M.D., late Professor of Chemistry, Materia Medica and Toxicology in Rush Medical College; and RALPH W. WEBSTER, M.D.; PH.D., Assistant Professor of Medical Jurisprudence in Rush Medical College. Second edition. Pp. 2242; 334 illustrations and 9 plates. Philadelphia and London: W. B. Saunders Company, 1923.

ALTHOUGH especially fitted for medico-legal purposes, yet this work is interesting and valuable to the practitioner as a reference book on many subjects. Psychiatry, for example, is here more satisfactorily dealt with than in many text-books devoted solely to this subject. Of especial interest is the discussion in the first volume of the physician's legal responsibility to patients receiving gratuitous treatment, of the conditions under which a physician may refuse or discontinue treatment, of the status of insane patients and of the physician's deportment on the witness stand. Almost the entire second volume is devoted to toxicology, and the subject is covered in a clear and comprehensive manner. This, the second edition, contains a number of articles by new contributors, and many of the articles in the first edition have been revised. Among the collaborators such names as Pearce Bailey, Da Costa, E. P. Davis, Dorland, Jelliffe, Allen J. Smith and Victor C. Vaughan speak sufficiently for the authoritative character of the work.

A.

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DISEASES OF THE SKIN. By ROBERT W. MACKENNA, M.A., M.D., B.CH. (Edin.), Honorary Dermatologist, Royal Infirmary, Liverpool; Honorary Dermatologist, The Children's Convalescent Home, West Kirby. Pp. 451; 166 illustrations. New York: William Wood & Co., 1923.

THE author has included in his book all the ordinary skin affections, while the rarer conditions are briefly mentioned in smaller type. Attention has been paid to the recent advances in dermatology and the possible part played in the etiology of skin affections by anaphylactic shock and foreign proteins. A classification has been adopted on etiology. Where the causal factor was undetermined the cutaneous affections are classed on their clinical appearances, with the exception that certain dermatological conditions are grouped together because of their association with some particular structure of the skin. The illustrations are excellent, the text well written and the large type and good paper add to the value of the publication.

K.

THE URETHRA AND THE URETHROSCOPE. By F. CARMINOW DOBLE, Hon. Casualty Out-patient Surgeon, St. Paul's Hospital, London, England. Pp. 120; 47 illustrations (2 in color). London: Henry Frowde, Hodder & Stoughton, 1923.

AN interesting little monograph upon a greatly neglected subject and one toward which more attention should be directed. The first third of the book is descriptive of instruments, with a short concise sketch of the normal anatomy. Concerning the instruments, it is to be regretted that the Montague, Holborn, Harrison, Campbell and Powell urethroscopes are little known in this country, and possibly they point with emphasis to the fact that we are somewhat neglectful of this field of diagnosis and unappreciative of its importance. The remainder of the book covers the special pathology and treatment of the anterior and posterior urethra, with an admirable chapter of fourteen pages on the female urethra, a valuable and novel addition. R.

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SUGGESTION AND COMMON SENSE. By R. ALLAN BENNETT, M.D. (Lond.), M.R.C.P., Torbay Hospital, Torquay. Pp. 105. New York: William Wood & Co., 1922.

IN a few entertaining and readable pages the author speculates upon the mechanisms through which suggestion may influence the body. He warns against the danger of mental dependency inherent in psychoanalysis and outlines a plan of suggestion which he has found useful in treating patients afflicted with both functional and organic disease. A.

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THE MEDICAL CLINICS OF NORTH AMERICA. ANN ARBOR NUMBER. Vol. VI., No. 5, March, 1923. Pp. 273; 23 illustrations. Philadelphia: W. B. Saunders Company, 1923.

THE Medical Clinics of North America in their travels around this continent arrived in Ann Arbor in the month of March. The result has been the production of a volume by the Ann Arbor clinicians which compares most favorably with the volumes that have been produced by the clinicians elsewhere in the United States. Such excellent clinics are given by the dozen different contributors that it would seem unfair to pick out any particular clinic for special mention. M.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**Diagnosis of Circulatory Diseases.**—In an endeavor to obtain complete diagnoses of cardiac conditions, WILLIAM St. LAWRENCE, Chairman of the Committee on Cardiac Clinics of the Association for the Prevention and Relief of Heart Disease, has drawn up a diagnostic outline in which every diagnosis of a cardiac disorder includes groups in the etiology, structural change, disturbances in pathological physiology and the functional capacity of the heart diagnosis. The diagnostic scheme thus outlined, in part is as follows:

*A. Etiology.* 1, Unknown; 2, "rheumatic:" *a*, acute rheumatic fever; *b*, chorea; *c*, growing pains; *d*, tonsillitis; *e*, pharyngitis; *f*, others, as purpura arhythmia nodosum, etc.; 3, syphilitic; 4, bacterial (specify bacterium if possible); 5, thyroid; 6, toxic: *a*, bacterial; *b*, mineral; *c*, vegetable (specify if possible); 7, neurogenic; 8, general systemic disease (specify the disease), *e. g.*, general arteriosclerosis; 9, traumatic.

*B. Structure.* 1, Atrophy of heart; 2, enlargement of heart; 3, hypertrophy of heart; 4, cardiac infarction; 5, rupture of heart; 6, cardiac thrombosis: *a*, auricle; *b*, ventricle; 7, myocarditis, acute; 8, myocarditis, chronic fibrous; 9, fatty infiltration; 10, fatty degeneration; 11, tumor of heart; 12, endocarditis: *a*, acute; *b*, chronic; 13, cardiac valvular disease: *a*, aortic insufficiency; *b*, aortic stenosis; *c*, mitral insufficiency; *d*, mitral stenosis; *e*, pulmonic stenosis; *f*, tricuspid stenosis; 14, congenital abnormality (specify lesion if possible); 15, pericarditis: *a*, acute; *b*, fibrinous; *c*, with effusion; *d*, pneumopericardium; 16, adherent pericardium; 17, pericardial effusion; 18, tumor of pericardium; 19, aortitis: *a*, without dilation; *b*, with dilation; 20, aneurysm of (specify affected vessel or heart); 21, embolism of (specify affected vessel); 22, thrombosis of (specify affected vessel); 23, arteriosclerosis, general; 24,

arteriosclerosis of (specify locality as, coronary arteries cerebral arteries, etc.); 25, arteries of (specify locality); 26, periarteritis of (specify locality); 27, no circulatory disease; 28, no cardiac disease; 29, undiagnosed.

*C. Pathological Physiology.* 1, Regular sinus rhythm; 2, vagal arrhythmia: *a*, sinus arrhythmia; *b*, sino-auricular block; *c*, simple bradycardia; *d*, ventricular escape; 3, premature contraction: *a*, auricular; *b*, nodal; *c*, ventricular; 4, simple tachycardia; 5, paroxysmal tachycardia: *a*, auricular; *b*, nodal; *c*, ventricular; 6, auricular flutter: *a*, paroxysmal; *b*, chronic; 7, auricular fibrillation: *a*, paroxysmal; *b*, chronic; 8, auriculo-ventricular heart-block: *a*, partial block, (1) prolonged conduction time, (2) dropped beats; *b*, complete block; 9, intra-ventricular block; 10, neurocirculatory asthenia; 11, valvular incompetency: *a*, mitral insufficiency; *b*, tricuspid insufficiency; *c*, pulmonic insufficiency; *d*, aortic insufficiency; 12, hypertension.

*D. Functional Capacity.* 1, Patients with organic disease, but able to carry on ordinary physical activity; 2, patients with organic disease, but unable to carry on ordinary physical activity: *a*, activity slightly limited; *b*, activity greatly limited; 3, patients with organic disease, but unable to carry on any physical activity, *i. e.*, who must remain in bed or in a chair.

*E. Patients with Abnormal Signs and Symptoms.* Not believed to be due to organic disease; this diagnosis to be "not cardiac—Class E."

*F. Potential Disease.* Patients without circulatory disease, but whom it is advisable to follow because of the presence or history of an etiologic factor.

**Xanthoma Diabeticorum.**—NICHOLSON (*Clifton Med. Bull.*, 1923, 9, 12) briefly reviews the literature, noting that the text-books on dermatology have articles on this condition while internists have apparently paid less attention to it. The case described is given in detail. A young man after symptoms of diabetes for a year developed small yellowish papular lesions especially over the extremities. On a strict diabetic regimen the skin lesion disappeared but due to lax adherence to diet when not under direct surveillance the diabetic condition grew worse and he succumbed in about sixteen months after appearance of the xanthomata. There was a marked upset in both sugar and fat metabolism, there being as much as 0.344 per cent blood sugar and 7 per cent blood fat at one time. There was some tendency for the rash to disappear as the blood fat decreased and to reappear as the fat increased.

**Quantitative and Qualitative Changes in the Island of Langerhans in Diabetes Mellitus.**—CONROY (*Jour. Metabol. Res.*, 1922, 2, 367) made an exhaustive study of multiple sections from serial blocks through the whole pancreas in 12 cases of diabetes and 12 controls of similar age, and a less thorough study of 95 routine autopsies of non-diabetics. In the diabetic group there was a marked reduction in the amount of insular tissue. The average number of islands per cross section was 73.6 as compared with 183.6 in the control series. Every case of diabetes showed more or less qualitative changes in the islands,

chiefly hyalinization and fibrosis, the latter lesion being quite widespread in some cases. A less marked hyalinization of the islands was seen in only 2 cases of the non-diabetic group. Changes involving the acinar tissue, particularly interacinar and interlobar fibrosis were seen in both series but were more marked in the diabetic series. He concludes that both quantitative and qualitative changes were operative in leading to a functional insufficiency of the insular tissue in diabetes.

**Studies on the Relation of Tetanus Bacilli in the Digestive Tract to Tetanus Antitoxin in the Blood.**—TENBROECK and BAUER (*Jour. Exp. Med.*, 1923, 37, 479) determined the amount of tetanus antitoxin in the blood of individuals harboring tetanus bacilli in their intestinal tract and of those whose feces contained none of these organisms. The sera of 26 individuals who showed tetanus bacilli in their feces all contained appreciable amounts of antitoxin while in only two of the sera of 30 tetanus-free individuals could any antitoxin be demonstrated. In a previous paper (*Jour. Exp. Med.*, 1922, 36, 261) they reported the isolation of *Bacillus tetanus* from the stools of 34 per cent of 78 individuals in Peking, China, and discussed the relation of this high carrier incidence to the apparently small number of tetanus infections in that country. They now conclude that an immunity is obtained by the growth of the organisms in the intestines which protects the individual against their growth in a wound. They suggest, although not yet recommending, this as a method of immunization against tetanus where such infections are liable to be common, as in trench warfare, although the danger of these individuals as carriers would have to be considered.

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## SURGERY

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UNDER THE CHARGE OF

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**Hernia Operations.**—HOGUET (*Surg., Gynec. and Obst.*, 1923, 37, 71) says that in a series of 827 inguinal herniæ in children there was no recurrence and no death. Three years of age is the usual or routine earliest age, but certain cases were operated in the first year of life when conditions demanded it. A larger series of adult inguinal herniæ has been done with recurrence in 1.6 per cent. Four deaths were noted in 963 operations, 1 of acute yellow atrophy of the liver in a man, aged forty-five years, where chloroform had been used; 1 in a man of eight-one years from cerebral embolism. In all these cases the Bassini operation was found to be most satisfactory. Seventy-six operations were performed for undescended testicle. The operation



of choice was the Bevan operation. There were no deaths in the series and no recurrence of hernia, but the testicular results were not uniformly good at any age. Cases with undeveloped scrotum gave the poorest results. The subject of direct hernia was very interesting, for in all cases of direct hernia an indirect sac can be found. There were 17 recurrences in a series of 259 direct herniæ. The Bassini operation and the Bassini operation with rectus transplantation were used. Femoral hernia was rare, for only 85 operations, or 3.4 per cent of the whole series, were done for this condition. The so-called purse-string operation was used for this series, with but 1 recurrence. Ventral postoperative or incisional hernia is not common. Thirty-four operations were performed with 1 death from pulmonary embolus and 1 recurrence. There were only 23 cases of strangulation seen among 2468 operations.

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**Surgery of the Hepatic and Common Bile Ducts.**—W. J. MAYO (*Lancet*, 1923, 1, 1299) says that the importance of removing all stones from the common duct cannot be overemphasized. In nearly one-third of the deaths which followed operations on the common duct in Mayo Clinic, postmortem examinations revealed that all stones had not been removed. The author suggests that some of the stones which are supposed to have reformed in the common duct are leftovers. In a period of twenty-two years, 104 patients were operated on for restoration of function between the hepatic and common duct, and the duodenum, with a hospital mortality of 15. The late mortality in all the years since operation was 19. Sixty-three of the living were followed with 45 well. Cases repaired at time of accidental injury showed no marked difficulty, for the tissues are normally pliable and if as much as 2 cm. of the ducts are lost the severed ends can be drawn together by end-to-end suture. The study showed that best results in secondary reconstruction were obtained from direct union of the stump of the hepatic duct and duodenum. Cholecystogastrostomy in malignant obstructions, whether in the head of the pancreas or the common duct, has proved a remarkably satisfactory operation. For benign disease cholecystoduodenostomy is preferable theoretically and it is usually practised in the Mayo Clinic. However, in several doubtful cases, which proved to be benign, cholecystogastrostomy has given good symptomatic results.

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**False Diverticula of the Jejunum.**—F. HELVESTINE (*Surg., Gynec. and Obst.*, 1923, 37, 1) says that acquired diverticula of the jejunum occur relatively rarely. Most cases are seen in old individuals. The diverticula in the majority of cases are of the false type and occur along the mesenteric border of the intestine. Intra-abdominal pressure, caused by rectal or vesical tenesmus is, perhaps, the force causing the development of the diverticula. Local traction upon the gut by adhesion, or by mesenteric vessels when shortened by sclerosis, is probably the initial cause of the formation of these diverticula in the author's cases. Acquired diverticula in the earliest stages of formation are of the true type and may continue to develop as true diverticula. In the majority of cases muscle fibers disappear by degeneration and the diverticula develop as false diverticula.

**Differentiation between Tuberculous and Non-tuberculous Inflammation of the Epididymis.**—STEVENS (*Jour. Urol.*, 1923, 10, 85) says that double epididymitis found on examination, slightly favors a diagnosis of tuberculosis, while prior orchidectomy or epididymectomy almost invariably means tuberculosis. A scrotal sinus of over a month's duration is probably tuberculous. Moreover, tuberculosis elsewhere in the body means genital tuberculosis in over 90 per cent of such cases. In cases of over one month's duration, the examiner has some help from the rectal examination. The older the lesion, the more does definite involvement of the prostate and vesicles point to tuberculosis; after six months this becomes a very marked factor for diagnosing tuberculosis. It must be emphasized that simple inflammatory changes of the epididymis may last as long as tuberculosis. There were 4 of the 35 non-tuberculous epididymitis cases who sought advice three years or more after onset of the swelling, and but 4 of the 74 tuberculous cases with a similarly long history in the author's series.

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**Quantitative Studies with Arsphenamine.**—KOLLS and YOUNG (*Johns Hopkins Hosp. Bull.*, 1923, 34, 181) say that approximately three-fourths of the arsphenamine injected leaves the blood stream in a few minutes after the completion of the injection. The remaining portion is rapidly reduced in amount, but traces may be found twenty-four hours later. The drug is stored in the liver, spleen, kidneys, lungs, cardiac and skeletal muscle. There is evidence that the alteration or excretion, or both processes perhaps, have appreciably reduced the amount of the drug three hours after injection. The liver is a more important excretory organ for arsphenamine and neoarsphenamine than the kidney. The brain shows a much lower concentration of drug in the experimental animal than does any other organ. The cerebrospinal fluid during the first twenty-four hours, if it contains the drug at all, does so only in minute concentration, which is too low to estimate with accuracy.

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**Roentgen Therapy.**—O'BRIEN (*Boston Med. and Surg. Jour.*, 1923, 189, 1) says the destruction of the tumor tissue by means of the radiation absorbed in it is the underlying principle of the new development in roentgen-ray therapy. Roentgen-ray of long wave length produced at low voltage—the so-called soft rays—burn the skin and do not penetrate deeply. Roentgen-rays of short wave length—the so-called hard rays—penetrate deeply and do not have the same tendency to burn the skin. Continental practice has not hesitated to give intensive treatments at one sitting, lasting six, ten and twelve hours. Some in America, who have tried to copy this method, have reported excellent results as to the disappearance of the malignant growths, but the patient has also disappeared. Repeated relatively small doses of roentgen-rays are to be preferred to the so-called intensive therapy of long duration, at one sitting, because of the stimulative effect on the lymphocytes and connective tissue, with general beneficial systemic effect.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**The Modification of Gastric Function by Means of Drugs.**—In this paper BENNETT (*Brit. Med. Jour.*, 1923, p. 366) collects the more recent experimental work concerning substances which have been demonstrated to affect gastric function. The agents may be divided into those whose chief action is on gastric secretion and those whose action is mainly on gastric motility. Atropine is the most effective drug for diminishing gastric secretion. Its hypodermic administration is less effective than its oral exhibition. The best results follow lavage of the stomach with very dilute solutions of atropine but a less laborious and almost equally satisfactory method of administration has recently been introduced by Bennett, namely, the administration of atropine in very small doses dissolved in a very large quantity of water. The action on the gastric mucosa is as definite as the action on the pupil. By washing the stomach with weak solutions of pilocarpine, it is possible to raise the HCl secretion but the absorption of the alkaloid soon leads to salivation and if the saliva is swallowed, the acidity of the gastric juice is reduced. The group of substances that neutralize the gastric juice after it has been secreted includes the alkaline salts. There is a considerable divergence of opinion as to the exact effects of sodium bicarbonate on secretion and acidity. Bennett's experiments led him to conclude that sodium bicarbonate, given before meals, causes an actual increase in the acid secretion after the meal, while if the alkali is administered later, the acid already secreted is neutralized; a period of neutrality lasting nearly an hour is followed by a rapid rise in gastric acidity to the original level. It would therefore appear that sodium bicarbonate tends to excite the gastric mucosa to increased secretion and that this effect more than counterbalances the neutralizing effect of the salt. Other alkaline salts, especially magnesium oxide and bismuth oxycarbonate, have a less stimulating effect, and weight for weight, magnesium oxide possesses the greater neutralizing power. In hyperacidity these salts should be administered at such periods after meals as will lead to their neutralizing effects coming into play without there being any possibility of their stimulating the gastric cells. For inhibiting secretion, atropine is far more efficacious than the alkaline salts. In gastric therapy, sodium bicarbonate finds its greatest usefulness in those rather rare cases where there is an excess of mucous and a low acid secretion. Hydrochloric acid is the most valuable agent for replacing a deficient acid secretion. It must be administered in rather larger doses (2 drams of the B. P. dilute acid) than are usually

recommended. There is no unimpeachable evidence that bitters have any marked effect on gastric function; there may be subjective impressions that appetite is improved but Carlson's studies show that the amount of food ingested is not considerably increased. Gastric motility is impaired by atropine and emptying of the stomach is somewhat delayed (rarely by more than fifteen minutes). In pylorospasm atropine often causes marked relief. Pilocarpine, on the other hand, increases gastric movements and hastens emptying of the stomach. The effects of strychnine on gastric motility are very interesting; in doses of 0.5 mg. gastric peristalsis is at first greatly increased and emptying of the stomach is accelerated; 1 mg. doses cause an initial increase in peristalsis but at the end of thirty minutes the contraction of the pars pylorica is sufficient to delay complete emptying of the stomach; with larger doses these symptoms are exaggerated and the net result is further delay in the emptying of the stomach.

#### The Properties of Certain "Colloidal" Preparations of Metals.—

A cursory survey of the literature dealing with the therapeutic action of metals in colloidal form gives the impression that they act as specific cures for every known disease. CLARK (*Brit. Med. Jour.*, 1923, p. 273) investigated the properties of some of the more widely advertised "colloidal" preparations. Dialysis and ultrafiltration experiments indicated that oscol ferrum and argentum were true colloidal solutions and were stable on exposure to air. Ultrafiltration experiments showed collosol antimonium and arsenicum and oscol arsenicum and stibium contain a mixture of colloidal and non-colloidal metal and on exposure to air all the metal tends to pass into true solution. Very little quinine in collosol quinine is in colloidal form and no demonstrable quantity of iron in collosol ferrum appears to be in colloidal form. In diffusion experiments oscol ferrum behaved like a colloidal solution but oscol iodine and collosol ferrum acted like non-colloidal solutions. Collosol and oscol iodine apparently suffer exactly the same fate in the body as does ordinary iodine; the "colloidal" preparations contain only traces of iodine (0.025 per cent of free iodine with 0.015 per cent of combined iodine) and are therefore not likely to induce iodism. Collosol and oscol arsenic and antimony were nearly as toxic as non-colloidal solutions on intravenous injection; they were only about half as poisonous on intramuscular injection because the organic matter in them hindered their absorption. Tartar emetic was superior to either collosol antimonium or oscol stibium as a trypanocidal agent and there was no demonstrable difference in the activity of arsenious acid and collosol arsenicum. The toxicity of the collosol preparations was about the same as that of the non-colloidal preparations of the same substances. Metals in colloidal form appear to exert only a feeble disinfectant action *in vitro* but if allowed to remain in contact with the bacteria for a prolonged period they acquire antiseptic properties because they are broken down and liberate free ions. There is no foundation for the claim that metals in colloidal form continue to circulate in the blood for a long time and act there as antiseptics. When administered intravenously colloidal metals produce a general reaction very like that following the injection of peptones or non-specific vaccines. This is a "protein shock" reaction and is due to the fact that collosol and oscol

preparations contain breakdown products of protein in considerable quantity as protective colloids. Our knowledge of the value of non-specific protein therapy is so vague that the fact that colloidal preparations may belong to this class gives little guidance to their therapeutic value.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Mongolism in One of Twins and the Etiology of Mongolism.**—HALBERTSMA (*Am. Jour. Dis. Child.*, 1923, 25, 350) reports 5 cases, and he thinks that all of these cases of mongolism idiocy resulted from so-called two-egg pregnancies. As is known, there are two types of twins. The one-egg, or identical twins, are derived from a single egg which has formed two embryos. They are always of the same sex, are enveloped in the same chorion and there is only one placenta. The children show marked resemblance. As the entire heritable nature is common to both, germinal affections will be equally present in both, as for example epilepsy and asthma. Acquired diseases, of which the causes may be sought in the condition, such as syphilis of the mother during pregnancy, will also manifest themselves in both twins. In the two-egg, or fraternal twins, there have been two eggs, which were fertilized separately. Each embryo is enveloped in a separate chorion, and they no more resemble each other or seem more closely related than ordinary brothers and sisters, and their sex may be different or the same. One of them may be affected by an inheritable disease, such as achondroplasia, while the other may be absolutely normal. Diseases of the mother that might affect the embryo, such as syphilis, will generally manifest themselves in both twins, although the symptoms may vary. If mongolism were not germinal in origin but acquired, then the occurrence of mongolism in one of twins would be a surprise. A review of the literature revealed 15 such cases and only 2 cases of mongolism in both twins. It would be difficult to imagine how one child could remain absolutely normal while the other showed the numerous and universal symptoms of mongolism. If the mongolism were due to defects inherent in the germ plasma the occurrence of mongolism in one of twins would be comprehensible, but it would only be possible in a two-egg pregnancy. All the cases in the literature had different sexes from the normal twins and were undoubtedly two-egg pregnancies. In the cases where both twins were mongolian idiots, it was only possible in one-egg pregnancies. It was interesting to note in the cases reported that only in two instances were the twins of the same sex.

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**The Treatment of Vascular Nævi with Radium.**—RULISON and McLEAN (*Am. Jour. Dis. Child.*, 1923, 25, 359) found that radium

therapy is expensive and time-consuming. There is also the chance of overtreatment, with subsequent ulcer formation and very tardy healing. The possibility that telangiectasia and atrophic skin may result, followed later by keratosis and epithelioma, has also been considered. The advantages of radium treatment are the freedom from pain, the very gradual changes in the lesion, which can be watched from treatment, and the probability of causing the lesion to disappear without appreciable damage to the overlying skin. In addition there is the advantage of rapid healing of ulcerations and hemorrhagic areas, the absence of scarring or when scarring is unavoidable the production of a smooth, supple and comparatively inconspicuous scar. It is possible to treat successfully lesions that because of their location are not suited for treatment by other procedures, as for example naevi of the eyelids or others on account of their depth and extent. Most potent of all reasons for using radium in treating angiomas is the fact that radium exerts a definite, specific, selective action on the abnormal endothelial cells lining the bloodvessels, which are at fault in the process. Not all angiomas respond equally well to radium treatment. The port-wine mark is very obstinate, since flat angiomas generally are more refractory than the raised. Many naevi of small size and situated on covered parts are easily destroyed by more rapid means.

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**The Schick Test.**—ZINGER (Am. Jour. Dis. Child., 1923, 25, 392) reports the results from more than 150,000 tests. A high percentage of positive Schick reactions was found among the children of the entering classes in the kindergarten and the primary grades. This varied in different schools from 60 to 85 per cent. The toxin-antitoxin injections could be given to these children without preliminary Schick testing. The schools located in the less congested sections of the city and attended by children of the more well to do showed, as a rule, from 100 to 200 per cent more Schick positive reactions than those located in the crowded sections and attended by children of the poorer classes. Repeated exposure to infections with the diphtheria bacillus is probably the most important factor in the development of a so-called natural immunity to the disease. Racial and hereditary family factors also play a role. Girls showed a somewhat larger percentage of positive Schicks than boys. They also showed more negative pseudo- and positive-combined reactions. This also held true for adults. The high percentage of positive Schick reactions among young children of the pre-school age may, under certain conditions, render it advisable to simplify the procedure of immunization by omitting the preliminary Schick test. These children should then receive three injections of toxin-antitoxin, but a supplementary Schick test should be performed after six months to prove the immunity.

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**Outlook of Nephritis in Children.**—ASHBY (Brit. Med. Jour., 1923, 1, 408) found that the occurrence of nephritis after scarlet fever varied in different epidemics, but it may be estimated at about 10 per cent. The outlook is usually good, and it is rare for the nephritis to become chronic. The amount of albumin in the urine does not seem to alter the outlook, for a patient with a large amount may get quite well while one with only a small amount may do badly. The worst cases are

those which have remained untreated for some days and those in which suppression of urine is present, as uremia is liable to occur. The preventive treatment consists in great care during the two or three weeks after the onset of the scarlet fever, especially as regards catching cold. In cases of acute nephritis the outlook is mostly bad. They run a course of from three months to two years, but complete restoration of health does not often occur. The child may get fairly well, but he is liable to further attacks which damage the kidneys still more until he becomes waterlogged and dies. Toward the end very little urine is passed, and dyspnea becomes a marked feature, so that the patient has to be propped up in bed. Uremic convulsions are also common.

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## DERMATOLOGY AND SYPHILIS

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UNDER THE CHARGE OF

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**Tryparsamide in Neurosyphilis.**—LORENZ, LOEVENHART, BLECKWENN and HODGES (*Jour. Am. Med. Assn.*, 1923, 80, 1497) report on the results of a prolonged and detailed study of the action of N-phenylglycineamide-p-arsonic acid (tryparsamide) upon neurosyphilis and particularly parietic neurosyphilis in man. The action of this drug is apparently not directly spirillicidal, but has to do rather with the resistance mechanism of the disease. It will be recalled, however, that Voegtlin and his co-workers have shown that the arsenic content of the spinal fluid after the administration of tryparsamide is higher than after the administration of any other arsenical. The technic of administration recommended by these authors consists of 3-gm. doses given weekly for a period of eight weeks, with intramuscular injections of mercury salicylate in 1-gr. doses, the latter being given weekly between the injections of tryparsamide. A rest period of from five to eight weeks between courses is given and two or three courses are employed in resistant cases. Relapse is more common when tryparsamide is used without mercury and may occur as late as two years after the institution of treatment, although the symptomatic improvement is remarkably persistent. Because of the pronounced constitutional benefits apparent during the treatment, the use of the drug is recommended in Wassermann-fast cases, in emaciated syphilitics and in those beyond middle age as well as in resistant neurosyphilis. There is a remarkable freedom from local or general reaction in the use of the drug which seems to permit its employment in cases which are reactive to other arsenicals. Stress must be laid on the fact that tryparsamide possesses the potentiality of injuring the optic tract and that it should not be used in cases showing degenerative changes in the optic nerves or retina. A careful examination of the eyes should precede any attempt to use the drug, and the development

of blurred vision during its employment is a signal for immediate cessation of the treatment. The preparation is not on the market, but is being employed by various observers under license of the Rockefeller Institute.

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**Gland Puncture in Syphilitics.**—OELZE (*Deutsch. med. Wchnschr.*, 1923, pp. 86-87) reports that he is unable to equal the 80 to 90 per cent positive puncture claimed by a number of authors. He cites Schultz, Sutton, Ebersson and Mitchell, who recommend various procedures. He has adopted the following technic: (1) Disinfect the shaved area with ether, alcohol, iodine; fix the gland between the forefinger and thumb of left hand; choose a moderately indurated gland. (2) Use a large gauge needle, with short bevel. (3) Use a 1 or 2 cc syringe with 0.25 to 0.5 cc physiological sodium chloride solution. (4) The needle is attached to the syringe and advanced into the gland. (5) The needle is turned several times within the gland. (6) The saline solution is then injected. (7) The syringe is disconnected from the needle and one waits two to five minutes turning the needle several times in the meantime. (8) The needle is again connected with the syringe and the contents of the gland aspirated. (9) The syringe with its contents are withdrawn and a few drops of the material are studied in the usual manner. Strict adherence to the finest details of the technic is necessary to obtain the greatest percentage of positive punctures. The method is of special value in diagnosing puzzling lesions that had had local treatment during the period when the Wassermann reaction is still negative.

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**The Wassermann Reaction in Pregnancy.**—HINTON (*Jour. Syph.*, 1923, 7, 155) discusses the results of the Wassermann reaction performed on the blood of 10,427 pregnant women in various Massachusetts hospitals. The method employed utilizes two cholesterinized antigens prepared from a plain alcoholic extract of human heart muscle and a more sensitive antigen also cholesterinized, made from guinea-pig hearts. Sheep's cells are used as the indicator substance. Employing this system, the author obtained 0.56 per cent positives in 3701 naval aviation students and 40.49 per cent positives in a penal group of 864 women. The proportion of positive results obtained in the 10,427 pregnant women examined was 4.18 per cent and doubtful results were obtained in 3.85 per cent. Studies of the cord blood indicate that it is only about one-third as effective in the detection of syphilis by the Wassermann test as that obtained by the usual venous puncture. Among the race groups, negroes lead the list of positives with the proportion of 33.3 per cent. Native Americans, Syrians, Portugese and Scotch stand next. The lowest percentages were among the Jews of native, Russian and Polish extraction and among the Swedes. The highest proportion of positives occurred in the age group of seventeen to twenty-two years. The author considers that a properly standardized cholesterinized antigen yields a negligible number of false positive reactions in child-bearing women.

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**Studies of the Wassermann Reaction on Syphilitic Exudates.**—STERN and RYPINS (*Jour. Lab. and Clin. Med.*, 1922, 8, 86) have



followed up the work of KLAUDER and KOLMER (*Arch. Dermat. and Syph.*, 1922, 5, 566) by a study of the local Wassermann reaction on the exudate from 34 demonstrated syphilitic primary lesions. In the majority of these cases, the blood Wassermann reaction was negative and secondary manifestations were absent. In all of the 34 cases, the local Wassermann reaction on the chancre exudate was positive in amounts as small as 0.0125 cc of serum. This very small amount of serum can be collected from practically any suspected lesion with a graduated capillary pipette so that the method is readily available under the conditions of ordinary practice. The surface of the lesion is sponged off with normal saline after which the lesion is dried and gently squeezed. If not enough serum is obtainable, slight scratching with the end of the glass capillary tube may be carried out, inasmuch as a small amount of blood does not affect the reaction. Local treatment of the lesions with a spirocheticide, while it may render the dark-field examination negative, does not appear to influence the local Wassermann reaction. The authors' observations appear to establish a local as well as a hematogenous site of origin for the specific complement-fixing bodies. The use of the local Wassermann is not proposed as a substitute for the dark field when this is positive, but when the dark field is not available or local treatment has been instituted the local Wassermann reaction has great value and may at times constitute the earliest means of obtaining a diagnosis.

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## OBSTETRICS

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UNDER THE CHARGE OF

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**A Mistaken Diagnosis and Its Result.**—SIGWART (*Zentralbl. f. Gynäk.*, 1922, 46, 1808) describes the case of a woman, aged twenty-three years, brought to the clinic with the history of an incomplete abortion and perforation of some portion of the abdominal or pelvic viscera. The patient was in wretched condition, the abdomen painful and distended; the pulse very rapid and so weak that it was felt with difficulty. The temperature was slightly subnormal. There was a slight discharge of blood from the vagina, and there were small lacerations and bruises about the vulva. On introducing the fingers in examination, they passed on the left side through an extensive tear into the abdominal cavity, and on opening the abdomen there was partially decomposed blood, which gave, on examination, a pure culture of streptococci. There was a general peritonitis present. At the fundus and posterior portion of the uterus there were three perforations. On the left side and behind the uterus was a mass which looked at first sight like the perforated large intestine, but on closer examination proved to be an emptied ovarian cyst. On removing this from its location the most

extensive injury to the uterus was found on the left posterior portion where the uterus was torn open freely. Total extirpation was performed, and it was found that the left uterine artery had been torn, and that there had been free bleeding. The patient died fifteen hours after operation. At autopsy, septic peritonitis and endocarditis with streptococcus infection were present. The case had been diagnosed as an early pregnancy and incomplete abortion, and the physician had dilated the uterus by several attempts, which were carried out in his office. Finally, with the aid of a midwife, it was decided to complete the abortion in the lodging of the patient. The midwife had given the anesthetic. The physician had introduced the hand when fluid escaped. In his efforts to empty the uterus as he supposed, the patient had become infected and death had followed. In commenting upon the case, it is remarked that a mistake in diagnosis between early pregnancy and a small ovarian cyst may readily be made. If in early pregnancy the uterus be in an abnormal situation, or if there be inflammatory conditions present, perforation of the uterus may readily be accomplished. A perfectly clear history of these cases is never obtained; but there is one point of criticism in the management of the case upon which the writer is emphatic. The practice of dilating the uterus or performing minor operative procedures upon these patients in the office of the physician is to be strongly condemned. If the case is complicated and accurate diagnosis is not made, no procedure can be safely and efficiently carried out, and such treatment is followed by disaster to both patient and physician.

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**Double Tubal Gestation, Operation, Recovery.**—AMARAL (*Gynec. et obst.*, 1922, No. 5, p. 319) describes the case of a multipara, aged twenty-nine years, whose general health had been good. She had had four children living and in good health, and her gestation and labors had been normal. There was irregular menstruation with metrorrhagia, followed by pain in the right iliac fossa, extending to the opposite side and down the thigh. There was a pronounced general disturbance and the hemorrhage became considerable. The patient expelled a small portion of material from the uterus with clots. On internal examination there was a small tumor on the left side, and on the right the condition could not be clearly made out. At operation both tubes were pregnant, and this was proven by the microscopical examination of the tissues after the removal.

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**The Action of Morphine and Scopolamine upon the Fetus.**—HORWITZ (*Lancet*, 1922, 2, 1303) endeavors to combat the statement frequently made that morphine and scopolamine tend to produce asphyxia in the fetus. On the contrary he states that in 500 deliveries under scopolamine but 1 child died during birth. He believes that where moderate doses are given that the child does not inspire too soon, and so does not inhale amniotic fluid, vaginal epithelium and bacteria from the genital tract of the mother. In this way mortality accompanying labor is reduced.

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**Coiling and Knotting of the Umbilical Cord.**—SELLHEIM (*Zentralbl. f. Gynäk.*, 1922, 46, 1746) reviews the various theories concerning the

developing of twisting, coiling and knotting of the umbilical cord. He speaks of what he calls the impulse to rotate, which originates in the pulsation of the cord, and states that the first beginnings of complications arise in the simple turning of the fetus or the umbilical cord upon its axis at its insertion. This resembles the situation which develops in an ovarian tumor or a tumor of the Fallopian tube. If the tension of the cord is somewhat lessened after this, the tendency is to develop coiling about the child, and this, he believes, is the second degree in the rotary motion. If the cord twists against the fetus or if the fetus is brought considerably against the cord, then will occur the development of coiling and knotting in proportion to the length of the cord and the conditions present.

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**Fibroid Tumor; Ovarian Cyst Complicating Pregnancy.**—In *Gyn-écologie et obstétrique*, 1922, No. 5, pp. 456, 549, SCHOCKAERT of Louvain reports two interesting cases. His first was a Cesarean hysterectomy for pregnancy, complicated by a fibroid tumor, which was in front of the presenting fetal part, making labor absolutely impossible. It was a fibroma prævia. Two excellent illustrations show this unusual condition. The patient's convalescence was complicated by sudden failure of the secretion of milk and severe headache, but otherwise she did well. The second case was that of a woman pregnant a month, who had a cyst of the left ovary, with twisted pedicle. The diagnosis in the case was not clear, for the history was very suggestive of tubal gestation. There was good reason for opening the abdomen, and at operation the diagnosis was apparent.

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**Stenosis of the Birth Canal Following Labor.**—STANCA (*Zentralbl. f. Gynäk.*, 1922, 46, 1769) reports two cases of this rare condition. The first followed extensive lacerations of the genital tract and a radical operation for the cure of cystocele and rectocele. After an effort had been made to open the vaginal canal by dilatation, a radical operation was performed, which was followed by a practical cure. His second case was a multipara, who after a confinement, had a chronic ulcer develop in the genital tract, which was treated by a midwife with concentrated solution of sulphate of copper. This ulcerated surface slowly healed, but produced complete atresia. The third case is reported following a confinement in which extensive laceration, without adequate repair, had occurred.

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**Glycemia and Glycosuria in Pregnancy and Their Diagnostic Value.**—DOSSENA (*Ann. di ostet.*, 1922, No. 10, p. 747) has made experiments to determine the diagnostic value of these conditions in pregnancy. His article is of considerable length and contains a review of the literature and description of different chemical methods employed in recognizing these substances. Glycosuria can be predicted by variations in the curve of glycemia, and such variations point to a deficiency in the function of the liver and modification of the equilibrium in the metabolism of pregnancy; and these factors are of some value in forming an idea of the integrity and functional capacity of the renal filter as regards its ability to permit the passage of sugar in solution.

## GYNECOLOGY

UNDER THE CHARGE OF

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**Carcinoma of the Cervical Stump.**—The startling figures on the incidence of cancer of the cervical stump has awakened the interest of DAVIS (*Boston Med. and Surg. Jour.*, 1923, 188, 304) in the subject to such an extent that he has reviewed all cases of cancer of the cervix that have entered the wards of the Massachusetts General Hospital for the five year period preceding January, 1922. There have been 123 such cases of which 8 or 6.5 per cent were cases of cancer of the cervical stump after supravaginal hysterectomy for fibroid tumors of the uterus. In these 8 cases carcinoma in the stump was detected at the following intervals after hysterectomy, twenty-four years in 1 case, fifteen years in 1 case, five years in 1 case, two years in 3 cases and less than one year in 2 cases. It is safe to assume that in the 3 cases in which cancer was found from five to twenty-four years after the original hysterectomy, that the disease was not present at the time of the first operation but was a new development. In the 5 other cases it seems quite probable that there was co-existent carcinoma at the time of the original operation. The histories show that in 2 cases a bloody vaginal discharge was noted almost immediately after the operation, in 1 case it was noted five months, in another ten months, and in the last, one year and eight months after operation. Pathological reports on the original growth were available in 4 cases, 3 of which showed simple fibromyoma, but in spite of this, vaginal bleeding was noted almost immediately after discharge in 1 case, after five months in 1 case, while in the other the first symptom of trouble was a foul vaginal discharge without blood appearing one year and eight months after operation. Davis believes that of the 4 cases which had their original operation in the Massachusetts General Hospital, cancer was present at the time of the original operation in 2 cases but was overlooked. That the occurrence of cancer in the retained stump bears little relation to the trauma of childbirth is shown by the fact that in 3 of the 8 cases the patients were single women. The explanation is undoubtedly to be found in the fact that these were cases of overlooked co-existent adenocarcinoma of the body of the uterus. The treatment which was instituted in these 8 cases of carcinoma of the stump consisted of radical excision of the stump by laparotomy in 2 cases; in 1 other case an attempted excision was abandoned on account of adhesions and the patient referred for radium treatment. In 2 cases the growth was cauterized and then referred for radium, while in 3 cases the patients

were directly referred for radium without any preliminary operative interference. The results of treatment have not been encouraging. In the 2 cases of excision the results of treatment are unknown, but of the 5 cases referred for radium treatment, 4 died of the disease within a year and a half while the sole survivor has well-marked evidence of extensive pelvic invasion. Carcinoma develops in the cervical stump in different ways. A co-existing adenocarcinoma of the body of the uterus which is overlooked in the original operation for fibroid tumor, may be the original focus from which the cervix is secondarily invaded. Davis believes that this is the commonest cause and accounts for at least one-half of his cases. A fibroid may have undergone so-called carcinomatous degeneration at the time of operation and act as a source of secondary infection of the retained cervix, or there may be independent but co-existent carcinoma of the cervix, either of the squamous-cell or the adenomatous-cell type which is overlooked at the time of the operation. Finally carcinoma, either squamous-cell or adenomatous-cell type may develop in the cervical stump after operation as a distinct entity. Combining all these forms of carcinoma, Davis assumes that the incidence of cancer of the cervical stump following supravaginal hysterectomy for fibroid tumors is 2 to 3 per cent or more, varying with the degree of accuracy with which cases of co-existent carcinoma are detected at the time of operation and the length of time that cases are kept under observation. How should this be met by the operating surgeon? Total removal of the uterus for fibroids is theoretically logical and correct, if the mortality rate is not thereby elevated above the percentage of incidence of the disease itself. A few experienced operators doubtless may be able to accomplish this, but in the hands of the average surgeon now doing supravaginal hysterectomy, the complete operation would undoubtedly elevate the mortality considerably above this point and there would be a considerable incidence of distressing complications in the way of vesical, ureteral and rectal fistulæ. Davis suggests that in every case in which hysterectomy is contemplated in the treatment of fibroids, the cervix should be inspected and the uterine cavity curetted as a preliminary measure, any suspicious tissue should be subjected to an immediate microscopical examination before any operation is performed. If the microscope reveals cancer, a total hysterectomy should be done. If no evidence of cancer is found a supravaginal hysterectomy may be done unless the appearance of the cervix arouses a strong clinical suspicion of malignancy. Only with increasing experience and skill should total hysterectomy be adopted by surgeons generally as a routine procedure. A careful follow-up system should be adopted for all cases of incomplete hysterectomy and patients warned that the reappearance of vaginal bleeding or discharge after operation calls for prompt examination. When cancer of the retained cervix does occur, its treatment is a serious problem. Early cases may be treated by radical abdominal excision, but the operation is even more formidable than the Wertheim operation itself. Radium undoubtedly offers the best chance in the great majority of cases.

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**Value of Ovarian Extracts.**—With the intention of establishing some definite method of determining the value of the various ovarian prepa-

rations, GEIST and HARRIS (*Endocrinology*, 1923, 7, 41) undertook an experimental investigation upon several ovarian extracts from four commercial laboratories. It is a well-established fact that after castration a definite atrophy of the uterus takes place, and it was with the idea of using this phenomenon as an indicator that the experiments were undertaken. They attempted to determine, if by the administration of these various preparations by intravenous injections, the atrophy could be prevented, minimized, or, if possible, hypertrophy could be obtained. At the same time, the breasts were also observed, as well as the thyroid, the hypophysis and the adrenals, to determine if the administration of these preparations had a definite effect upon any of them. Controls were made by subjecting animals to the same operative procedures, but without administering the drugs. The ovaries and a small portion of the tubes were removed from rabbits without interfering with the blood supply to the uterus. At the same time a small segment of the uterus near the horn was removed as a control and one breast also. Before operation the animals were weighed, and when they had recovered from the operation, after a period of usually forty-eight hours, they were put on the same food as before operation. In all cases the uterus showed atrophy, although not so marked in those killed early as in those permitted to live for two to three months. The breasts, as the uterus, showed marked atrophy. There is an actual diminution in the size of the organ, with a disappearance of the secretory gland tissue and a collapse and diminution in the caliber of the ducts. The pituitary gland did not show much change, while the thyroids of the injected cases appeared somewhat enlarged with a tendency toward the formation of small cysts in a few cases. There was an average loss of 16 per cent in body weight. Analyzing their results, they find that the injection of commercial ovarian extracts does not prevent the atrophy of the uterus following castration in rabbits, therefore there is nothing in these preparations sufficiently active that will substitute for the hormone that normally maintains the nutrition of the uterus.

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## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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The Relationship of the Orange and White Pyogenic Staphylococci with Special Reference to Vaccine Therapy.—The value of vaccine therapy in staphylococcus infections is now generally acknowledged.

Most experienced workers deprecate the use of stock vaccines and claim that only autogenous vaccines yield good results. Inasmuch as local conditions made the use of stock vaccines for the treatment of staphylococcic infections imperative, KLIGLER and KRAUSE (*Jour. Infect. Dis.*, 1923, 32, 133) examined thirty-five strains of staphylococci culturally and serologically with a view to determining certain type strains, from which an effective polyvalent stock vaccine could be prepared. The strains were isolated mainly from furuncles, abscesses, mastitis and acne. Although certain quantitative cultural differences existed, it was not possible on the basis of these characters alone to differentiate the pathogenic staphylococci into distinct types. The results of the serological tests performed by agglutination and absorption reactions, employing immunized rabbit serums, indicated that there was a definite group relationship between the orange and white staphylococcus, but that the aureus serums were more specific and did not agglutinate the albus strains to the extent which the serums of the latter agglutinated the aureus cocci. The absorption tests confirmed the conclusions based on the agglutination tests, namely, that the two pigment types were related. Both types of cocci produced group agglutinins for orange and white cocci, but there was a distinct difference between the two varieties—the aureus being a more homogeneous and defined type. With these facts at hand, polyvalent vaccines were made from two main types of orange and two strains of white staphylococcus. It was found that these stock vaccines were as effective therapeutically as were autogenous vaccines.

**Immunity Studies of Rocky Mountain Spotted Fever: I. Usefulness of Immune Serum in Suppressing an Impending Infection.**—For the past twenty years Rocky Mountain spotted fever has been the subject of study by many investigators. As a result, it has been proved that the disease is transmitted to man by a certain wood tick, which receives the virus from infected wild rodents, especially gophers and jack-rabbits. Ricketts was the first to transmit the disease from man to guinea-pigs and monkeys by injecting the blood drawn from spotted-fever patients, and having fed normal ticks on the infected guinea-pigs, to reproduce the disease again to normal guinea-pigs by allowing the infected ticks to feed on the animals. Previous attempts by Ricketts and Gomez to enhance the potency of a serum which would protect against the virus by repeatedly injecting the immune animal with virus having been unsuccessful, NOGUCHI (*Jour. Exper. Med.*, 1923, 37, 383) conducted a series of experiments with the idea of producing “an immune serum of at least sufficient potency to be useful when the time of infection is definitely known and the injection of serum can be made soon after the inoculation of the virus, as when a laboratory worker is bitten by an infected tick or accidentally inoculates himself with an instrument charged with infected material.” By inoculating the serum of rabbits, immunized by an attack of the disease plus a reinforcing infection two weeks after recovery, into guinea-pigs after the injection of the virus and at the end of twenty-four, forty-eight, seventy-two and ninety-six hours, and five, six and seven days, it was found that the early administration of such an immune serum will prevent the virus from multiplying and causing

fatal infection. When the immune rabbit serum was given to the infected guinea-pigs within the period of incubation the suppression of the infection was insured, but after the onset of symptoms the serum exerted no beneficial effect. In view of the high titer of the immune rabbit serum and of the comparative susceptibility of man and the guinea-pig, the author recommends that 0.2 cc of the serum per kilo of body weight be injected immediately after the inoculation, preferably intravenously. For the average adult about 16 cc should be given.

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**Incidence of Hemolytic Streptococci in Normal Preputial Secretions in Men.**—PILOT and BRAMS (*Jour. Infect. Dis.*, 1923, 32, 172) were able to isolate and identify hemolytic streptococci from the preputial sac of 9 out of 100 normal men from twenty to forty years of age who did not exhibit genital lesions. The individuals examined were from the poorer walks of life. The streptococci always occurred in small numbers and presented the characteristics of *Streptococcus pyogenes*. They were somewhat less pathogenic than streptococci isolated from tonsils and adenoids. Staphylococci were encountered in large numbers constantly in the cultures from the preputial secretions. The coccal flora of the preputial sac resembled that of most moist hairy regions of the body. The authors state that "In analyzing the data now available as to the distribution of hemolytic streptococci in normal persons, we must recognize that their occurrence in regions other than mouth is unusual, and that the most constant habitat is the oro- and nasopharynx, particularly in the crypts of the tonsils."

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**Intestinal Antisepsis: Effect of Antiseptics on a Type of Experimental Toxemia.**—Having previously demonstrated that the toxins, whose absorption is responsible for the toxemia following acute intestinal obstruction, are produced chiefly by the activity of the proteolytic group of intestinal bacteria, DRAGSTEDT, DRAGSTEDT and NISBET (*Jour. Lab. and Clin. Med.*, 1922, 8, 190) conducted over 100 experiments on dogs to ascertain the effect of various antiseptics on the bacterial flora of closed intestinal segments. These isolated segments of the upper jejunum were made by dividing the bowel in two places from 8 to 12 inches apart and then reuniting the proximal and distal intestine around the isolated segment, care being taken not to injure the blood supply to the segment. In most cases the intestinal segment was first thoroughly washed with water and then with the antiseptic to be tested. The category of antiseptics employed included ether, alcohol (70 per cent), lysol (2 per cent), silver nitrate (5 per cent), thymol (10 per cent), Dakin's solution, betanaphthol, mercuric chloride and saturated solutions of zinc chloride, salol or quinine sulphate. Approximately, 90 per cent of the animals died within a week following the operation and at autopsy there was found usually a marked distention and perforation of the perforated loop with general peritonitis. Although these materials were applied directly to the segment of intestine in their given strength undiluted or mixed with gastric or intestinal content, it was not possible to secure a sterilization or to prevent the intestinal toxemia as produced under the conditions of these experiments.



## HYGIENE AND PUBLIC HEALTH

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A Study of Malaria Prevalence and Some of the Factors Affecting it in the Sikeston Area of Southeast Missouri.—ZIEGLER and MAXCY (*Pub. Health Repts.*, 1923, 38, 237), in discussing their survey, point out that malaria is still an important problem, though the incidence is on the decline. In one locality 15 per cent of persons had malaria each year. The tenant farmer is held partly responsible, due to the shifting nature of this population and the consequent lack of interest in improvement. The last paragraph of the paper contains the following useful suggestions: At present, efforts to reduce malaria morbidity should center chiefly about the individual home and the school. The people must be educated to the role of the mosquito in transmission and its life history and habits; also how properly to screen their homes and the value of keeping them tightly screened, and how to "hand-catch" the adults that rest in bedrooms by day. Some provision for more adequate medical attention must be made. Quinine must be popularized in place of the inadequate "chill tonics" and the "standard treatment" should be introduced in order to diminish the percentage of "carriers."

Tuberculosis: A Chapter of a Forthcoming Report of the Committee on Municipal Health Department Practice of the American Public Health Association.—WINSLOW and BAKER (*Am. Rev. Tuberc.*, 1922, 6, 960) state that perhaps the most remarkable feature brought out by this study is the fact that while efficient antituberculosis work is carried on in nearly all cities by some agency, the municipal health department plays, in most cases, a very small part in this important field of public health. In only 46 out of 83 cities are there municipal tuberculosis clinics; in only 45 are there tuberculosis nurses; in only 29 has the health department any specific appropriation definitely ear-marked for tuberculosis work; and in only 13 is there a separate bureau of tuberculosis and in only 6 a full-time director. The budgetary allotment for 23 cities having a definite allowance is 4.9 cents *per capita*. The authors believe that every health department in a city of 100,000 population should include on its staff an expert, specifically charged with the supervision and coördination of the campaign against the most deadly of preventable diseases, for whatever aid may be offered by private agencies the strategy of a widely conceived antituberculosis movement can be fully executed only by

the official health authorities of the community. Sixty-six of the 83 cities studied have a law requiring the reporting and registration of tuberculosis. The enforcement of the law is far from complete, however, since of 69 cities for which data was collected, 40 show less than 2 cases reported per annual death and only 8 show more than 3 cases per annual death. Four or 5 cases per annual death would be a reasonable standard. Practically all cities have an antispitting law, but only 13 report arrests. Thirty-four cities have a law for the isolation of the wilfully careless consumptive, but only 8 report action taken under this statute. In 37 of the 77 cities where data are available, municipal health departments conduct tuberculosis clinics, and in 9 cities clinic provisions are secured by other municipal agencies, 5 of the first and 2 of the second group having private clinics in addition. Eleven cities have state or county supervised clinics, in some instances coöperating with private or municipal agencies. Private organizations alone provide 20 cities with clinic facilities. The number of sessions per clinic averages 4.7 per week, and 2.7 per week per 100,000 population. Evening sessions are held in 12 cities. The average number of physicians engaged in tuberculosis clinic service is 1.5 per 100,000 population. From the statements available, it appears that approximately 10 per cent of the total number of physicians render whole-time service. In several cities the medical service is voluntary. Until a paid medical service is provided the best results will not be obtained from the clinic as a factor in the antituberculosis movement. The average number of nurses engaged in tuberculosis clinic work is 2.3 per 100,000 population. In those instances where specialized tuberculosis work is carried out by the Health Department, a slightly higher rate, or 2.7 per 100,000, is found. The ratio of both physicians and nurses to population is far too low for adequate results. The average number of annual visits to tuberculosis clinics per 100,000 population is 2228. This somewhat surprisingly high figure is due to the work accomplished in the larger cities. For 41 cities below 250,000 population the average visits per year per 100,000 population amount only to 1432. The average number of visits per patient per year, on the other hand, is only 2.8, and the average number per new patients is 6.9. An average of less than 3 visits per patient per year seems to reflect a distinct lack of efficiency in holding the patient. The average cost of clinic service per visit and per patient is \$1.84 and \$4.76 respectively. Institutional facilities for the treatment of tuberculosis are made available for city cases through municipal departments of health, hospitals, the state, the county or private organizations. The average number of institutional beds available for city tuberculosis patients per 100,000 population is 59.6, or 1 bed for approximately every 2 annual deaths, as against the usual standard of 1 bed per every annual tuberculosis death. The percentage of these beds occupied averaged 78. The admission rate to hospitals and sanatoria is 64 per 100,000 population, or 52.9 per 100 annual deaths. As is well known, the condition of the patient on admission to the hospital or sanatorium is, in a large measure, advanced. In the present study about 60 per cent were in the advanced stage and about 17 per cent in the incipient. The average length of stay by the patient was 6.2 months, a rather good figure; and the cost per patient per day averages \$2.25. Sixty-

four cities report active follow-up work of discharged arrested cases and 50 cities claim to carry on this work until the termination of the case. The visiting nurse and the public health nurse play a most important part in this work. Sixteen cities out of 28 state that the follow-up work is done by the local visiting nurse or public health nurse association. Various methods for vocational rehabilitation of arrested cases are provided by 26 cities. Over one-half of the cities carry on special antituberculosis activities and treatment measures, as is illustrated by the fact that 30 cities have open-air schools or classrooms and 25 have camps of various types. In general, then, it may be concluded that antituberculosis work in the large cities of the United States shows encouraging progress along the lines of dispensary and sanatorium treatment and of public health nursing, but a much more extensive department is needed. The municipal health department has, however, been notably backward in taking the position of leadership which properly belongs to it. The larger cities in general show much more efficient machinery for dealing with this problem than the smaller ones. The appointment of a competent director of antituberculosis work under the municipal department of health would be a most important step in coördinating the activities of existing agencies and filling gaps, in ensuring the provision of adequate dispensary and nursing and sanatorium service, and in securing the treatment of a larger proportion of patients in the curable stages of the disease.

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#### **Carbon Tetrachloride in the Treatment of Hookworm Disease.—**

LAMBERT (*Jour. Amer. Med. Assn.*, 1922, 79, 2055) states the following as a result of his studies: (1) Carbon tetrachloride is a vermifuge and vermicide of great potency; (2) it gives little discomfort to the patient; (3) it permits of rapidly treating, at a low cost, vast populations suffering from hookworm disease; (4) reëxamination of the feces of 823 treated patients indicated that one treatment administered to each individual in a given area had lowered the original infection rate of 100 per cent to less than 9 per cent; (5) clinically, the standard of health of the community is immediately raised.

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All communications should be addressed to—

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ORIGINAL ARTICLES.

**ERYTHREMIA (POLYCYTHEMIA RUBRA VERA).**

THE DEVELOPMENT OF ANEMIA; THE RELATION TO LEUKEMIA;  
CONSIDERATION OF THE BASAL METABOLISM, BLOOD  
FORMATION AND DESTRUCTION AND FRAGILITY  
OF THE RED CELLS.\*

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POLYCYTHEMIA rubra vera (Vaquez-Osler disease), appropriately termed erythremia by Osler<sup>1</sup> and others, is recognized as a disease due to excessive erythroblastic activity of the bone-marrow. This disorder, primarily of the red cell elements of the marrow, is comparable to that of the white cell elements of the marrow known as chronic myelogenous leukemia. Both conditions may be looked upon as neoplasms of the hemopoietic tissue.

**Blood Formation.** The excessive activity of the bone-marrow in erythremia is evidenced by the fact that cases upon which a careful autopsy has been performed have shown great increase in the amount of red marrow which is actively hyperplastic and

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which may be altered in character from normal. Evidence of the increased activity of the marrow is shown in the living subject by the presence of both abnormal and immature red cells in the circulation. In the literature, one not infrequently finds the statement that the blood is essentially normal and that immature red cells are seldom seen. It has been our experience, however, in accord with that of many others, always to find the red cells changed from normal, and in most instances to observe evidence of immaturity. This statement is based upon observations made upon 15 cases, and the blood of some has been studied many times over a period of seven years. The change from normal may, however, be slight, and consist of only a little unusual variation in size, with an occasional polychromatophilic red cell. Greater changes are often seen, a feature being an unevenness in the depth to which the cells take the stain, dependent, we believe, upon cells

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#### BLOOD OF ERYTHREMIA.

The preparations were stained with Wright's stain. The variation produced by staining in the actual color of the red cells of the different preparations has been inevitable. The actual color difference of preparations is of no import. It is important to note the distribution of the color and the variations seen in the same blood.

The drawings were made by aid of a camera lucida under 970 magnifications.

The actual (except No. 5) fields especially illustrate the red cells from 6 cases of erythremia. The blood numbered seven is from a normal individual. Increases of bone-marrow white cells were present in all of the patients and the platelets usually increased.

1. The blood a few months before death of the case with anemia, which did not come to autopsy, referred to in the text. Note the macrocytosis, the blasts and polychromatophilia. Microcytes were rare. Red count 2,500,000 per cm., hemoglobin, 55 per cent.

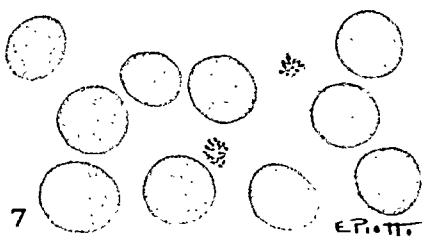
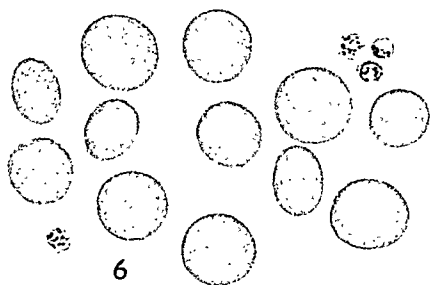
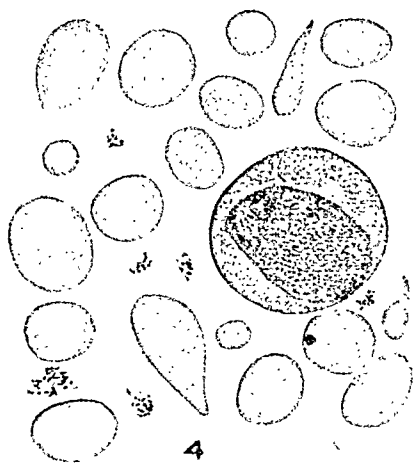
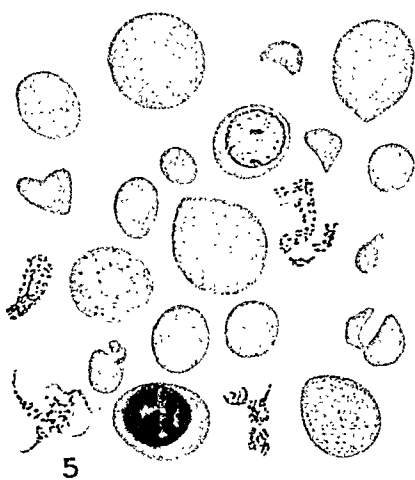
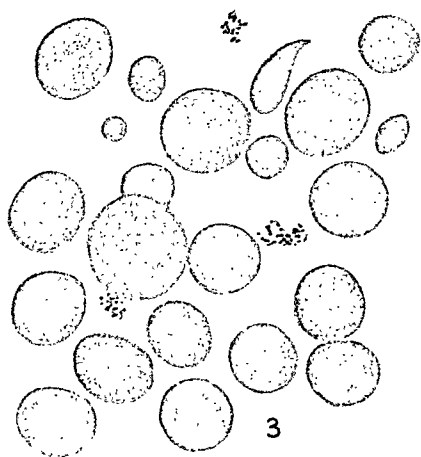
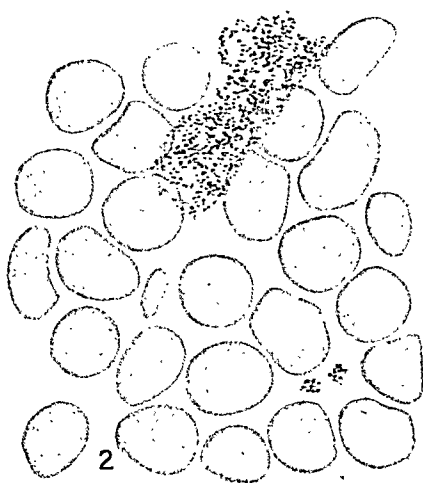
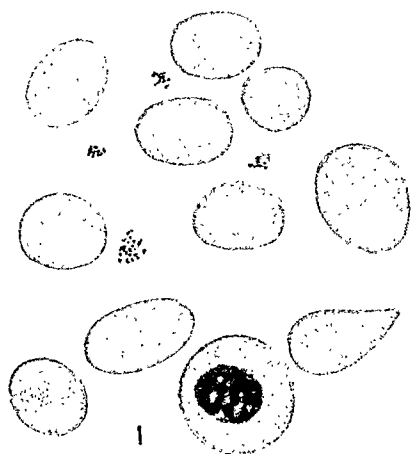
2. From a case with a red cell count of 10,000,000 per cm. and a hemoglobin of 180 per cent. Increased viscosity, a feature of polycythemic blood, makes the preparation of smears difficult. This is evidenced here by the flattening out of the cells. Faint polychromatophilia and unevenness in depth of staining is shown. Microcytes occur but are rare. An agglutinated mass of platelets is present.

3. This patient had a red cell count of 8,500,000 per cm. and hemoglobin 105 per cent. Note the achromia, the variation in size, the varying degree of polychromatophilia. Blasts, not shown in this field, rarely occurred, as did an occasional myelocyte.

4. A field of cells from the case with anemia that is living, referred to in the text. Red count 3,300,000 per cm., hemoglobin 88 per cent. Cells of many sizes and shapes, including megalocytes and microcytes, are present; some deeply stained, others achromic. Polychromatophilia is evident. Blasts were plentiful. Howell-Jolly bodies were rare, one appears in this field. Immature white cells were common, a very immature one is shown.

5. The blood, one year before death, of the case with anemia that came to autopsy, as referred to in the text. Red count 4,100,000 per cm., hemoglobin 70 per cent. This drawing represents cells which appeared in two adjacent oil immersion fields. It shows the actual average variation in size and shape. There are brought into the field cells showing different signs of immaturity. Note the stippling, ring-like body, polychromatophilia and blast. The latter were numerous and many immature white cells present.

6. Note the variation in size and variation in color of the red cells. Slightly polychromatophilic cells occur. The grayer color of all the cells, as compared to the normal ones (7) is due to a difference in the stain. The red count 6,850,000 per cm., hemoglobin 140 per cent.



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of different ages. Achromia may be marked, and great variations in the relation of the hemoglobin to the red count occur with the color index less than 1. At times there appear many cells showing polychromatophilia; some very deeply and others very slightly basophilic. Macrocytes and microcytes may occur in varying numbers and proportions. Blasts not infrequently occur. Yet in some instances reticulated red cells (young cells) may be actually decreased, as occurs in experimental polycythemia, as noted by Robertson,<sup>2</sup> and Krumbhaar and Chanutin,<sup>23</sup> and as we have observed at the height of remissions in pernicious anemia. It is to be realized that the numbers of young red cells entering the peripheral blood depend upon the state of the marrow at the moment, and that their presence or absence does not indicate the fundamental character of the marrow.

Further evidence of increased activity of the marrow in erythremia is shown by the leukogenic elements sharing in the process, as is witnessed post mortem by increase of the leukoblastic tissue. This leukoblastic activity is reflected in the peripheral blood by the almost constant finding of an increased white count and an increased percentage of bone-marrow leukocytes. It is not uncommon to find a few, and occasionally many, immature white cells in the circulation. The detailed appearance of the polymorphonuclear cells as well as the immature cells may deviate from normal, as shown by variations in their size and by the character of their cytoplasmic granulations and nucleus. These features are of a type one may associate with hasty or abnormal formation.

The platelet elements of the marrow may also become involved in the disease process, in a similar fashion as they do in myelogenous leukemia. They may be increased in the blood stream, and even megacaryocyte nuclei may enter the circulation.

Plate I illustrates the character of the peripheral blood in erythremia, especially the erythrocytes.

In myelogenous leukemia, looked upon by many as a form of neoplasm, the abnormal proliferation in the marrow is readily reflected in the peripheral blood. It is argued by some (Ward<sup>3</sup>) that, because the peripheral blood in erythremia shows only occasionally such immature cells as blasts and that because extra medullary blood formation is often lacking, the proliferative process in this disease does not appear disorderly enough to support the theory that it is in the nature of a neoplasm.

It is recognized that it is easier to influence the output of white-cell elements from the marrow than it is the red-cell elements. It is not necessary to assume that blasts and many immature red cells must appear in the circulation in order to conceive that erythremia is in the nature of a neoplasm. The immature elements will appear according to the rate of growth-pressure of the marrow, as shown by Drinker.<sup>4,5</sup> From our studies, it is evident that,



especially in cases of long duration and with the development of actual anemia, a very disorderly type of blood formation with extramedullary hematopoiesis may occur and be reflected in the peripheral blood. This would favor the conception that the disease is in the nature of a malignant hyperplasia.

It is reasonable to assume that signs of a very disorderly marrow are usually not observed, because it requires a long period of time before the condition becomes sufficiently pathological to permit a marked abnormality in the types of cells delivered from the marrow. Often before the condition reaches such a stage, patients may die from various results of the polycythemia *per se*. This situation is, perhaps, comparable to what occurs in pernicious anemia, in which there is a gross departure from normal blood formation. If the peripheral blood or the marrow be examined in the height of remission or early in pernicious anemia, but little abnormality is observed, this transitory finding being in contrast to the so-called megaloblastic reaction, which is often extreme and observed in relapses.<sup>6</sup>

**Cases Developing Anemia.** Among the 15 cases of erythremia are 3 that have developed definite anemia and have served to clarify further our conception of this disease. These 3 cases were exceedingly similar; 2 are now dead, 1 having come to autopsy. These cases, all women, had polycythemia (the red count being above 7,000,000 per cm. and frequently as high as 11,000,000 per cm.) with some splenic enlargement for a period of five years in 1, and for eighteen to twenty years in the other 2 cases. During this time they suffered from all of the usual and some of the unusual symptoms of the disease. In the course of about a year following the many years of polycythemia, the red counts of all 3 patients dropped, and the hemoglobin decreased to a relatively greater degree. The red cells fell to about 5,000,000 per cm., and the hemoglobin (calculated from the oxygen capacity) to about 85 per cent. Either coincident with or shortly following this drop, the spleens increased considerably in size, so that they then filled at least the whole left side of the abdomen. In 1 case this change occurred two years before death; in another, about six years before the postmortem examination. In the third who is now living in a reasonable state of health, the change took place about two years ago. In all cases, the red counts and particularly the hemoglobin continued to fall, although over a period of weeks a definite increase of the count to 8,000,000 per cm., followed by a further rapid decline to 3,000,000 per cm., occurred in the case that had the disease the shortest time.

Shortly before the death of 2 of the patients the red count was about 2,500,000 per cm. In the third case (now living), the count is 3,500,000 per cm. In all cases coincident with the development of the anemia, striking pathological changes were observed in the

peripheral blood. During the period of anemia the red cells showed marked variation in size and considerable variation in shape. Microcytes were evident, though never in profusion. Macrocytes of abnormal shapes occurred, and true megalocytes. In one blood these were very plentiful, so that the red-cell picture resembled that of a typical case of pernicious anemia, while the red-cell picture in all 3 cases suggested this disease. The unevenness in the depth of staining of the cells was usually striking. The numbers of polychromatophilic cells varied, as did the reticulocytes. Considerable increases were frequently observed. Various types of nuclear remains were present. Blasts were a feature; as many as 3000 per cm. were seen. All types were present, including some showing divided nuclei. With progression of the disease, more of these immature elements appeared in the blood stream.

The white-cell picture was one that may be seen in myelogenous leukemia. As the disease advanced, the white count tended to become higher and averaged 35,000 per cmm. From time to time fluctuations occurred, occasionally being quite extreme. All forms of immature myelogenous white cells appeared, some of which conformed to no standard type. The lymphocytes were distinctly few. It was not uncommon to see 10 per cent of myelocytes, sometimes more, while even myeloblasts reaching as high as 15 per cent were observed. During the anemic phase, the platelets fluctuated from distinctly above to even below normal. Free bits of megacaryocyte cytoplasm occurred, as well as occasionally a megacaryocyte nucleus.

The patients presented numerous features that are not commented upon here, as they are not distinctly related to the fundamental nature of their disease, except for the fact that all showed some enlargement of the liver.

Extramedullary blood formation has been reported in erythremia, with partial myeloid transformation of the spleen in some cases, but perhaps not to the degree found in our case. Dr. Wolbach has made a detailed examination of the tissue in the case that came to autopsy. This patient had suffered from her disease some twenty odd years. The spleen weighed 3200 gm. It presented a remarkable picture of myeloid transformation, which intimately resembled that of myelogenous leukemia. The liver also had the appearance of a leukemic liver of a myelogenous type. Signs of red cell formation in clumps of myelocytes were found to a less extent in the lungs, some of lymph nodes and adrenals. The marrow was actively erythroblastic, and was filled with an excess of myelocytes and immature elements. Megacaryocytes were abundant. The 2 cases that have not come to autopsy would appear to be entirely similar to this one that did.

**Relation of Erythremia to Leukemia.** The resemblance of erythremia to leukemia has already been alluded to. From the clinical

observations, the case that came to autopsy seems unquestionably one of erythremia, and the pathological findings that intimately resemble those of leukemia heavily support the hypothesis that the condition is analogous to this latter disease and that they bear a close relationship. Previously, we<sup>7</sup> have referred to this relationship, as have others.<sup>8 9 10</sup> Blumenthal's<sup>11</sup> well-known case of polycythemia, with many myelocytes in the peripheral blood and the finding at autopsy of excessive leukoblastic activity, has often been referred to in such discussions.

As mentioned before, some relatively slight degree of myelocytosis is often present with polycythemia, and the leukoblastic elements of the marrow are increased and involved in the disease process. A few other cases are recorded that resemble Blumenthal's and our 3 cases referred to, with marked alteration in the formation of white cells. Rosin's<sup>12</sup> case, Herxheimer's<sup>13</sup> and Brieger and Forsbach's<sup>13a</sup> are examples that terminated with all the typical features of myelogenous leukemia. One of us has observed also a man who had a red cell count between 6,500,000 and 7,500,000 per cm. and a white cell count of about 20,000 per cm., with 15 per cent myelocytes, die a year later with marked anemia and the peripheral blood of leukemia. The typical findings of this disease were present at autopsy.

That a patient with typical leukemia may develop a distinct polycythemia is recorded in the literature, as shown by Winter<sup>14</sup> and also Ghiron's<sup>15</sup> case. It may be emphasized here that the megacaryocyte elements of the marrow share in the disease process of leukemia and erythremia, and that rarely in the former condition they may be relatively more involved than the white cells.<sup>16</sup> In such a condition, the blood may be flooded with megacaryocytes and their derivatives, the platelets, so that for the time the disease process appears to be particularly confined to the megacaryocytes, as erythremia is to the red cells and leukemia to the white cells. The term piastrinemia has been given by Pianese<sup>17</sup> and Di Guglielmo<sup>18</sup> to such a condition. It thus appears that there occur cases of erythremia or leukemia that illustrate multiple varieties of varying degrees of primary pathological activity of myeloid tissue which usually conforms to a definite type.

**Basal Metabolism in Erythremia.** Before discussing blood destruction and the cause of anemia in erythremia, observations upon the basal metabolism will be referred to, because the increased metabolism that has been found is believed to be related to the pathological blood formation. There are but few records in the literature of the basal metabolism in erythremia; and so far but few determinations have been made in our cases. Abbott<sup>19</sup> found in 1 case the basal metabolic rate to be +16 per cent on one occasion, and +27.8 per cent five months later. Marsh<sup>20</sup> found +21 per cent in a case. Isaacs<sup>21</sup> has noted a basal metabolism of +35.2

per cent, on the average of several determinations, in a case with the red cell count remaining at about 9,000,000 per cm. The basal metabolism in our case with anemia that came to autopsy varied between +10 and +20 per cent two to four years before death. Six months before death it was +40 per cent. Two determinations on the other patient, who died with anemia, gave figures of +60 and +50 per cent at about the time the anemia began to develop. The patient who is now living and who has anemia with a leukemic blood picture has had a basal metabolism of +50 to +35 per cent. Six observations\* on 4 cases of erythremia with polycythemia have shown an average basal metabolism of +21 per cent, the extremes being +10 and +35 per cent.

Gunderson,<sup>22</sup> at the Huntington Hospital, has indicated that the increased basal metabolism found in myelogenous leukemia may be dependent upon the abnormal blood formation, it being higher the greater the immaturity of the cells in the peripheral blood. On account of the relationship between these two diseases, it is believed that the increased metabolic rate in erythremia is intimately related to the increased active blood formation. Our cases with the highest rates showed greater bone-marrow activity than those with the lower rates. This view, that increase of metabolism is associated with an increased rate of blood formation, can be reconciled with the view given by Isaacs,<sup>21</sup> who suggests that it is dependent upon the liberation of an excess of nuclear material formed in the increased production of red cells.

**Blood Destruction and Consideration of Cause of Anemia in Erythremia.** In erythremia, the actual levels of the red cells and hemoglobin may vary markedly within a brief period of time, due especially to vasomotor activity. They also may vary markedly in periods of weeks or months, due presumably to variations in the equilibrium between blood formation and blood destruction. That such remissions and relapses may occur is not well recognized. It is important to do so when judging the effect of therapeutic measures.

There is no evidence that the increase of red cells is primarily due to a decreased rate of destruction. One may readily conceive that the organism with polycythemia strives to compensate for the increased blood formation and to remove the excess of blood by increased activity of the process of blood destruction. The development of anemia following polycythemia may be explained on the ground that overcompensation occurs, the hemocidal process becoming excessive so that anemia ensues. The anemia may also be explained as being dependent upon some alteration in the type of blood formation.

There is scant reference in the literature to blood destruction

\* We are indebted to Dr. J. H. Means for some of the metabolic rate determinations.

in erythremia. During life an increased output of urobilin has been noted, and microcytosis may be a feature. Thus, some increased blood destruction may at times occur in erythremia; and our observations further support this view. On the average, the 3 cases with anemia appeared slightly sallow. A few isolated observations on their plasma showed it to contain a slight excess of bile pigments. The output of urobilin in the stools was found to be increased to two to three times above normal. These observations, as well as the occurrence of microcytes, suggest that abnormal blood destruction was present.

Experimentally, it has been shown by Krumbhaar and Chanutin<sup>23</sup> and others that following experimental polycythemia, induced by repeated transfusions of blood, there may develop an anemia with increased number of young red cells in the circulation. There occurs an increased output of urobilin during the stage of polycythemia, and a still greater increase with the development of anemia. Such an experimental condition may appear comparable to the clinical cases referred to. Increased blood destruction may account for the anemia in these animals but, as discussed below, it does not seem to be the chief cause for the anemia in the three individuals referred to above.

It is recognized that the spleen is deeply implicated in the process of blood destruction, and it is attractive to assume that its enlargement in erythremia may be associated with an increased amount of blood destruction. The increase in size of our patients' spleens coincident with the development of the anemia might be considered as dependent upon an increase of hemolysis that produced the anemia. If such was the case one would expect to find at postmortem considerable evidence of blood destruction.

Postmortem observations concerning blood destruction in erythremia are very meagre. It has been reported<sup>8</sup> that increased phagocytosis may occur, but it is evident from a few available reports that this is not the rule. Weber<sup>8</sup> and others believe that the splenic enlargement in polycythemia vera is at least partially due to hyperplasia of the splenic pulp associated with increased hemolysis, and that the enlargement cannot be wholly accounted for by the partial myeloid transformation seen in some cases, or by the presence of erythroblastic foci. Engorgement with blood accounts for some of the enlargement.

The postmortem examination of our cases revealed no unusual amount of phagocytosis in different parts of the body, and there appeared to be no increase of pigment deposit. There was thus no postmortem evidence of excessive blood destruction. However, clinical signs of abnormal blood destruction were obtained, but there was no evidence that this was more than slight. It thus seems distinctly improbable that this patient's progressive anemia was fundamentally dependent upon excessive hemolysis.

The anemia may be explained on the grounds that following years of an abnormally excessive erythroblastic activity, the response of the marrow succumbed to the strain and became most disorderly with the proliferation of immature leukoblastic and other elements as occurs in myelogenous leukemia. This degenerative proliferation will readily account for the progressive enlargement of the spleen and liver in this individual. However, from reported autopsy observations, as well as from 3 additional cases that Minot has observed post mortem, it seems that the splenic enlargement of many cases of erythremia can be only partially, and sometimes not at all, accounted for by myeloid foci or metaplasia. There is not a complete understanding of the hypertrophy as Weber<sup>8</sup> has indicated.

Another form of altered blood formation other than an embryonic hyperplastic type may account for development of anemia in erythremia. Freund's<sup>24</sup> case suggests that where the cause of the disease permitted at first stimulation, it later was so "toxic" that cessation of blood formation resulted. His case of polycythemia gradually developed the blood picture of pernicious anemia and an aplastic marrow was found post mortem. The effect of anti-syphilitic measures may have influenced this patient's marrow.

Excessive irradiation leads to anemia, and one may appropriately wonder if such therapy had produced the anemia in our cases. They had been treated by radium, but it is not believed that radiation enhanced the anemia or caused the leukemic-like blood picture which these patients developed. The increase in the size of the spleen and the distinct drop in the red cell count occurred in the 2 cases that died prior to any radiation. The one that did not come to autopsy showed the further temporary distinct rise in the red cell and hemoglobin level, and this followed four doses, each of about 3000 mc. hours, of radium irradiation over the spleen, given some weeks apart. Only one further radiation treatment was given, this being only 3000 mc. hours, at a time when the count was 3,500,000 per cm., eight months before death. A few radium irradiations of 3000 to 5000 mc. hours were given some months apart to the patient that came to autopsy. These appeared to help the patient symptomatically, but distinct alterations in the blood did not occur except for a tendency to decrease for a time the numbers of immature bone-marrow cells. The third patient, who is living, received irradiation at least two years prior to the increase in size of the spleen with the development of anemia. During two years prior to this event, relatively small doses of roentgen-ray were given, followed at that time by decrease in the size of the spleen.

**Further Consideration of Blood Destruction.** Tileston,<sup>22</sup> in his résumé upon hemolytic jaundice, refers to the fact that cases of erythremia in the terminal stage may exhibit a leukemic blood

picture and develop an anemia and thus simulate cases of the former disorder. This is certainly true, and though excessive blood destruction does not wholly account for the development of anemia in erythremia, it most probably does so in hemolytic jaundice. However, it does appear from clinical observations alluded to above and from data given below that an increase of blood destruction varying from time to time does occur in erythremia. It is believed that such is the case, because both an increased output of urobilin and an excess of microcytes may occur. Likewise, as referred to later, the alterations in the fragility of the red cells and the hemolytic properties of the serum further support such a view.

In some cases with polycythemia that may or may not be cases of true erythremia, excess of blood destruction seems to account for the development of an anerythremic phase. This is indicated particularly by the report of cases that have shown the features of chronic acquired hemolytic jaundice,<sup>8, 26</sup> including increased fragility of the erythrocytes to hypotonic salt solution. We have also observed one case of quite typical hemolytic jaundice, that had some anemia, develop a red count for over a year of about 7,000,000 per cm., with the hemoglobin about 110 per cent. Both the maximal and minimal resistance of the red cells to salt solution remained diminished. This is in contrast to our observations of the fragility in undoubted erythremia reported below, where the minimal resistance was never diminished.

Increases in the output of urobilin are not necessarily dependent upon an excess of blood destruction. Even so, blood destruction is characteristically associated with such an increase. A few isolated reports, such as those of Eppinger and Charnas,<sup>27</sup> Bauman,<sup>28</sup> Giffin *et al.*,<sup>29</sup> Wilbur and Addis,<sup>30</sup> upon the output of urobilin in erythremia are to be found in the literature. None shows a decrease. The majority show some increase, but this is rarely marked. The few estimations that we have made have always shown at least a slight absolute increase.

Twelve determinations of the urobilin output in the stools by the method utilized by Robertson,<sup>31</sup> in 6 cases with the red cells elevated about 7,000,000 per cm., gave 10,000 dilution units as the lowest figure and 27,000 as the highest. (The upper limits of normal are considered 8000 dilution units.) Urobilinogen and urobilin were present in increased amounts in the urine of some of these cases. One observation, a year before death, on the case with anemia that came to autopsy showed the fecal urobilin to be 15,000 dilution units, while an isolated observation on the living case with anemia gave 33,000. Consecutive observations over a long period of time have not been adequately made, though in the case that developed anemia that did not come to autopsy six determinations were made over a period of two years. When the

red cell count was about 6,000,000 per cm. there was a urobilin output averaging 18,000 dilution units; with anemia this figure increased, so that when the red count was in the vicinity of 3,500,000 per cm., a figure of 25,000 dilutions was obtained. It is evident, therefore, that the output of urobilin may be essentially no more marked in cases with anemia than when polycythemia is present. Chester M. Jones,<sup>32</sup> in his study of the bile pigment output in the duodenum, has pointed out that, though the actual pigment figures may be above normal, the figures when considered in relation to the red cell count may be below the normal average. Thus, the process of blood destruction in erythremia, as judged by such figures, may be no greater than normal for the number of red cells present. Dr. Jones has kindly determined from the duodenal contents the bile pigment output in 3 of our cases with marked polycythemia. In 1, the average output was 323 dilution units, the normal figure being but little over 100. Urobilinogen was present in an abnormal amount. The other 2 cases showed 220 and 190 dilution units for the average pigment in the duodenal contents. No urobilinogen was present. An analysis of the data suggests that following the time when the highest figures were obtained, the red cells and hemoglobin tended to fall; they at least did not rise, as was the case in some instances when the output of urobilin in relation to the red count was not increased. No definite relationship of the urobilin output to the fragility of the red cells has been determined, though it would appear as if an initial onset of hemolysis in more concentrated salt solution than normal was particularly to be found with distinct increases of the urobilin output. Distinct increase of the urobilin output, however, occurred without such alteration in red cell fragility.

Microcyte formation, particularly when the cells show tailing and signs suggesting fragmentation, may be considered as dependent upon increased blood destruction.<sup>33</sup> We have observed the presence of many microcytes in some instances of erythremia with high counts, while a few such cells are frequently to be observed in the blood of these patients. At times in erythremia no microcytes are observed, while at other times in the same case they appear.

In the cases that developed anemia, microcytes were constantly found, though they never appeared in very excessive numbers, and at times were scant. Thus, fluctuation in microcyte formation occurs in this disease, as does fluctuation in the output of urobilin. The relationship between these two factors cannot be adequately correlated from the data at hand. It is not unreasonable to assume that fluctuation of both microcyte formation and urobilin output indicates alteration in the degree and intensity of blood destruction in this disease. Such an increase may be looked upon as Nature's effort at compensation for the excess of blood,



and account for some but not all of the fluctuations that occur in the level of the red cells and hemoglobin.

**Fragility of the Red Cells.** The influence of the polycythemic process on the red corpuscles is shown by the behavior of these cells when placed in hypotonic sodium chloride solution and in hypotonic blood serum.

**A. TO SALT SOLUTION:** The few reported investigations of the fragility of red corpuscles to salt solutions in erythremia often show abnormal but varying results which are difficult to reconcile. Normal, increased and decreased, maximal and minimal resistance is reported. The results are chiefly concerned with isolated cases and no very complete studies have been made. Weber,<sup>8</sup> Marsh<sup>20</sup> and some others have recorded the occurrence of a normal fragility, while several have noted increase of fragility, particularly Höglér<sup>34</sup> and Gutzeit.<sup>35</sup> Höglér<sup>34</sup> reports cases with a slight increased maximal resistance, but with a normal minimal resistance, as well as cases with normal resistance. Gutzeit<sup>35</sup> studied the fragility in 5 cases. He observed combinations of increased maximal and minimal resistance, and increased maximal and decreased minimal resistance. Following radiation, there occurred a decrease of the maximal resistance. His figures show a lengthening of the resistance range: On the other hand, distinct diminution in the fragility of the red cells may occur as reported, for example, by Ward,<sup>36</sup> Isaacs,<sup>21</sup> Bensis<sup>37</sup> and Marsh.<sup>20</sup>

In our series of 15 cases of erythremia, we have noted, also, variations in the fragility of the red corpuscles when tested against hypotonic sodium chloride solutions. The normal values for concentrations of sodium chloride in which hemolysis is first observed and in which it is complete are 0.42 per cent and 0.28 per cent respectively. The upper normal limit for the difference between the per cent salt solution in which initial and complete hemolysis occurs is 0.15. With these figures in mind, we note the following abnormalities:

1. A lengthening of the resistance range (span); that is, a greater than normal difference between the concentration in which hemolysis begins and the concentration in which it is complete.

2. An increased fragility of the red corpuscles; that is, beginning hemolysis in a concentration of sodium chloride definitely greater than 0.42 per cent, with complete hemolysis at the normal point or in weaker salt solution than normal.

3. Complete hemolysis occurring in a concentration of sodium chloride definitely lower than 0.28 per cent, with a normal, increased or decreased initial hemolysis.

4. A "trickling effect," by which we mean a slow onset of hemolysis; a slight, but definite, occurrence of hemolysis in high concentrations of sodium chloride, with marked hemolysis occurring in not far from the same concentration as seen in the case of normal

cells which normally is close and not far from the very beginning of hemolysis.

These abnormalities are not characteristic of erythremia, but are probably related to alterations in blood production and perhaps blood destruction.

In 40 observations upon 15 cases of erythremia, an increased resistance range was noted in 10 cases. Four cases showed a span of over 0.2, the highest figure recorded being 0.34. In no case was the span abnormally short. Six observations upon 1 case and 5 observations on 2 others over a period of four years showed a tendency for the resistance range to increase from the vicinity of 0.15 to 0.2 or greater as time went by. A definite increase in the concentration of the solution in which initial hemolysis occurred was noted in 6 cases, as shown by 16 tests. This varied between 0.54 per cent and 0.46 per cent, and there was a tendency for the same case to show a similar initial hemolysis in spite of marked variation in the red cell count and hemoglobin. With the increase of initial hemolysis, the complete hemolysis occurred at least at the normal point, and 12 of the tests showed it to be complete in abnormally low concentrations, it being 0.18 per cent in 1 instance and 0.2 per cent in 4 others. Three cases showed a decrease of initial hemolysis, it being 0.38 per cent or 0.36 per cent, complete hemolysis occurring from 0.18 per cent to 0.26 per cent. The "trickling effect" was particularly seen in the cases with increased fragility, though observed in some others.

B. TO DILUTIONS OF SERA: In the literature, one finds isolated observations upon the fragility of the red cells by other methods than hypotonic salt solution. For example, Pickard<sup>38</sup> noted increased resistance to antihuman amboceptor, which decreased as the patient's red count dropped, leading him to the conclusion that the anerythremic phase was dependent upon an increase of hemolysis. Lutenbacher<sup>39</sup> and Freund and Rexford<sup>40</sup> each found in 1 instance no hemolytic property of the polycythemic serum. From the results of various tests of fragility of the erythrocytes and allied but incomplete data, several, including Herrnseier,<sup>41</sup> have deduced hypotheses to suggest that in erythremia increases and decreases of the rate of blood destruction occur. One must recognize that the mechanism of such tests must greatly deviate from the actual state of affairs within the body.

We have investigated also the resistance of the red corpuscles in another way, previously described by one of us.<sup>42</sup> By this method, the resistance of the red corpuscles is tested simultaneously against hypotonic sodium chloride solution, dilutions of the patient's own serum and dilutions of the serum of a normal individual of the same iso-agglutination group. At the same time, the resistance of the normal red corpuscles is tested against dilutions of the patient's serum. With this method, 18 observations have

been made on 9 different patients. The outstanding abnormalities shown are of two types, as follows:

1. A tendency toward an abnormally long resistance span in the mixture of patient's cells and patient's serum, and in the mixture of patient's cells and normal serum. Normally, this resistance span in such tests is not over 0.2. In all but 1 case, the resistance span of the patient's cells in dilutions of the patient's serum was, on at least 1 observation, above this figure, and above it in 13 of 18 observations. The greatest span was 0.7, and 7 observations showed it to be between 0.38 and 0.46. There were but 8 tests with patient's cells and normal serum. These showed the span to be distinctly shorter than when the patient's cells were mixed with dilutions of their own serum. There was, however, a tendency for it to be slightly longer than normal by about 0.04. Dilutions of the patient's serum did not alter the resistance span of normal cells.

2. The second form of abnormality noted was a concentration of soluble serum constituents corresponding to an abnormally high concentration of sodium chloride permitting initial hemolysis—that is, increased fragility of the red corpuscles—in the case of mixtures of patient's cells and patient's serum, in the case of patient's cells in normal serum, and in the case of normal cells in patient's serum.

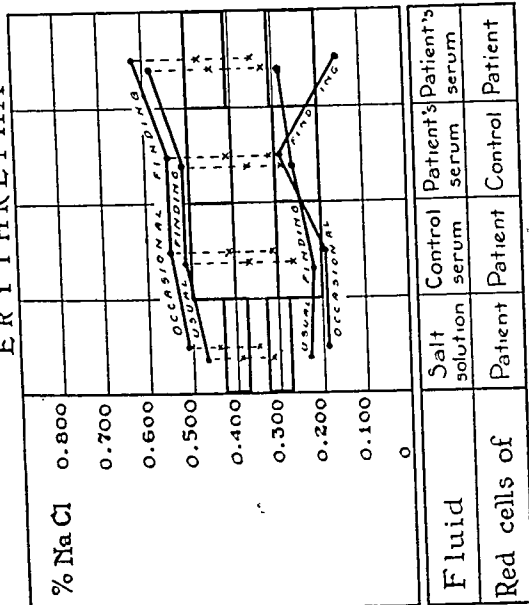
Four of the 9 patients showed on at least one occasion an increased fragility of their corpuscles when placed in their own serum. When more than 2 tests were made, some months apart, changes from an increased to a decreased fragility were observed, possibly dependent upon therapy, as suggested by Gutzeit.<sup>35</sup>

The shift in the dilutions of serum from the normal initial hemolysis of the equivalent of 0.5 per cent sodium chloride was as marked as to begin in 0.9 per cent, though usually in 0.54 per cent to 0.6 per cent. In 2 instances the initial hemolysis was found to be somewhat decreased. When the fragility of the cells was increased in their own serum, it was increased when tested against normal serum. The degree of increase was, however, distinctly not so marked. Six tests were made of normal cells with 6 different patients' sera. They showed a definite tendency to become hemolyzed in a lesser dilution, increased hemolysis, than in their own serum.

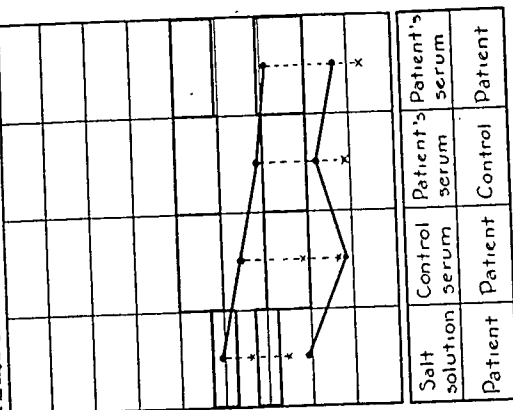
These various serum fragility tests did not run parallel with those made with salt solutions. It was true, however, that if the salt fragility test showed increased initial hemolysis or a long resistance span, the test with dilutions of the patient's serum and his own cells showed a similar state of affairs. However, gross alterations in this latter test occurred without alterations in the former.

Chart I with its legend shows examples of the abnormalities

# FRAGILITY OF RED CELLS HEMOLYTIC JAUNDICE



# ANEMIA DUE TO BLOOD LOSS



## CHART I.

Heavy rectangles indicate limits of variations in concentrations corresponding to beginning and complete hemolysis in the normal. On vertical dotted lines, distance from dot on continuous black line to first cross represents maximal normal resistance span; distance to second cross represents corresponding to beginning and complete hemolysis in a given case. Dots on continuous heavy lines represent concentrations corresponding to beginning and complete hemolysis in the normal.

The chart shows the alterations in the fragility of the red cells in the usual cases of erythremia as well as an illustration of the most markedly abnormal findings. It does not show the other forms of these alterations, nor the fact that normal findings may occur, as noted in the text. A contrast between blood loss findings and those observed in certain cases of hemolytic jaundice and chronic anemia due to repeated blood loss is also shown.

referred to above, and contrasts the findings in some cases of hemolytic jaundice and many cases of chronic anemia due to repeated blood loss. The chart does not show an example of the more normal findings that may occur in erythremia, or an instance where the initial hemolysis begins in less concentrated salt solution than normal.

C. SIGNIFICANCE OF THE FRAGILITY TESTS: In evaluating the results of these various tests, one naturally first endeavors to associate them either with other laboratory data or a clinical condition of the same patients. Yet our own data and the observations reported in the literature do not seem to warrant the conclusion, at present, that any definite and undoubted relation exists between the clinical condition of the patient or other laboratory data and the results of various fragility tests. One is forced, for the present, to set forth a hypothesis in order to correlate the findings.

It is to be recollected that alterations in red cell fragility may be due to a variety of causes. Changes in the carbon-dioxide content of the blood may produce alterations as noted by Stadie and Van Slyke,<sup>43</sup> and by Greenthal and O'Donnell.<sup>44</sup> The fluctuations following exercise noted by Libermann and Accl<sup>45</sup> might be due to such a cause, or might be dependent upon changes in the destruction of cells which may occur following exercise, as noted by Broun.<sup>46</sup> It would seem as if, besides the direct influence of chemical substances on the fragility, fundamental changes in the character of the cells dependent upon their manner of production or destruction would affect their resistance.

However, as Rous<sup>33</sup> has pointed out, many investigators have attempted to show that alteration of the fragility of the red cells gives an indication of their age, although others have been unable to bring forth any evidence to substantiate this theory. There is no available means of determining the relative age of erythrocytes, except in the case of relatively very young ones. Some believe increased fragility is dependent upon an excess of mature cells, while others, as Meulengracht,<sup>47</sup> believe this is a sign of youth. From the statements made below, together with such studies as those of Rusznyák and Barát<sup>48</sup> and Schustrow and Wlados,<sup>49</sup> it is probable that increased resistance, especially the maximal, is affiliated with immature cells.

One must be impressed with the constancy of the results of fragility tests performed on normal red cells; likewise with the fact that the resistance span becomes shorter than normal<sup>42 50 51</sup> in cases in which the bone-marrow shows fatty aplasia and thus ceases to discharge cells into the circulation; and hence in cases in which presumably the red cells tend to approach the same age.

Moreover, there has been noted<sup>52</sup> a distinct tendency to a lengthening of the resistance span, with particularly a diminution of the

point at which complete hemolysis occurred in salt solution in cases of prolonged chronic anemia, due to blood loss, as well as from other known causes in which distinct hyperplasia of marrow occurs. Slight decrease in initial hemolysis usually occurred. Similar results<sup>52</sup> have been obtained in rabbits following experimental chronic anemia due to blood loss. In spite of the fact that Pepper and Peet<sup>53</sup> and Key<sup>54</sup> have considered that reticulated cells are neither more nor less fragile than adult cells, it has seemed to us from certain observations concerning the effect of solutions upon reticulated cells observed under the microscope that they may be more resistant than adult cells. It is not intended to give here a full discussion regarding the production of cells and their fragility. It, however, has seemed to us from what has been said above, together with a careful consideration of much literature, that an increased resistance span, and particularly an increase of the maximal resistance (less concentrated salt solution), is associated with an active hyperplastic marrow, which probably permits cells of many ages to appear in the circulation, particularly immature ones, though not necessarily immature enough to show reticulation.

In erythremia the peripheral blood contains cells of a wider age range than normal, at least during certain phases of the disease, as shown by histological studies. This, perhaps, may be further manifested by the increased length of the resistance span. The concentration of salt in which initially complete hemolysis occurs may quite possibly shift upward or downward respectively according to whether there is a preponderance of old or young cells present.

The increase of initial hemolysis (increase of fragility) may be dependent upon the numbers of old cells that are present. The "trickling effect" might indicate the presence of excessive numbers of old cells in the blood, the bulk of the cells being of the same mean age as are those of a normal individual. An increased fragility is often associated with conditions in which undoubted alterations in blood destruction occur, chronic hemolytic jaundice being the classical example. There is only indirect evidence that increased fragility may be due to excessively old or a predominance of old red cells, while there is some evidence at hand, as given by Pearce,<sup>55</sup> to suggest that their diminished resistance is related to increased hemolysis due to an augmentation of splenic activity. The recent observations of Bolt and Heeres<sup>56</sup> further indicate that the spleen has the power of diminishing the osmotic resistance of the erythrocytes, as shown by testing blood before and after coming in contact with it. This organ, as well as others, may prepare cells for hemolysis, as suggested long ago by Bottazzi,<sup>57</sup> cells so affected when tested by different methods may break up with greater ease than normal. Increased hemocidal properties of the serum are not necessarily to be found if one recognizes that

the cell may be prepared for hemolysis by the action of an organ. It thus seems not unreasonable to assume that increase of the concentration, in which initial hemolysis occurs with or without decrease of the point of complete hemolysis, is dependent upon all or some of the cells in the body having been subjected to the influence of a hemolytic process. With this variation, the resistance span not only may be lengthened if cells of widely different ages are present, but also may be in an abnormal range, as occurs in hemolytic jaundice. In such a disease, alterations of fragility might depend upon a pathologically formed cell.

Thus, the point of view is offered that increase of fragility is especially dependent upon cells that have been damaged in some manner, as by a hemolytic process, and that decrease of hemolysis, especially the point of complete hemolysis, is associated with some form of immature cells, not necessarily reticulated. A predominance of old cells may influence the character of the result of a fragility test, and a long span is indicative of the presence of cells of many ages.

It is thus possible that a patient with erythremia may show a normal resistance span within normal limits or any of the variations mentioned above, depending upon the state of balance between the rate of delivery of relatively young cells to the blood and the rate or method of removal of cells.

Our data also bring out another point: That humoral factors may play an important part in blood destruction in erythremia. As indicated, normal red corpuscles begin to hemolyze at higher concentrations when mixed with the serum of some patients suffering from erythremia than they do when mixed with the serum of a normal person. The serum appears to exert a hemolytic influence on the red cells. The same is reported by Buckman and Horrall<sup>58</sup> in the case of serum from persons suffering from pernicious anemia and *Streptococcus hemolyticus* septicemia. This is in sharp contrast to the results obtained in certain cases of hemolytic jaundice, where the sera behave normally, and in certain cases of anemia following blood loss, where it appears that the serum develops a sparing influence on the red cells. It is interesting to note, too, that although there is usually an increased resistance span in the case of mixtures of the erythremic patient's cells and serum, this span approaches normal dimensions in the case of normal cells tested against the serum of patients suffering with erythremia, even though hemolysis does tend to begin at a high concentration.

Presumably, one is dealing with two opposing factors: Increased production of red corpuscles tending to flood the blood with cells, which if not destroyed would inevitably result in the presence of an increased number of cells of all ages, and at the same time a compensatory hemolytic process tending to destroy the red cells.

As a result of the former, one would expect a lengthened resistance span with hemolysis being complete in a relatively low concentration (due to young cells), and perhaps beginning at a relatively high concentration, due to a sufficient number of old cells. A hemolytic influence, as that of the spleen, might cause an increase of initial hemolysis to be observed with or without augmented hemocidal activity of the serum. So far as is known, there is no evidence to contradict such an explanation and the data at hand in part substantiate it.

**Summary.** 1. Certain aspects of erythremia are presented from a study of 15 cases.

2. The increased activity of the marrow in erythremia is reflected in the peripheral blood by increases of all three formed elements originating from it—erythrocytes, leukocytes and platelets. It is evidenced likewise by the appearance of abnormal and immature forms of all three elements, which may occur in greatly augmented numbers. The blood picture may then resemble that of myelogenous leukemia.

3. Three cases are recorded that, after having polycythemia for many years, developed anemia, coincident with a further increase in the size of the spleen and a leukemic blood picture. One of these cases was examined post mortem. The spleen, liver and bone-marrow showed a hyperplastic blood formation very similar to that seen in myelogenous leukemia.

4. Myelogenous leukemia and erythremia appear intimately related, and both may be of a neoplastic nature. There occur cases of erythremia and leukemia that illustrate multiple varieties of varying degrees of primary pathological activity of the myeloid tissue, which usually conforms to a definite type.

5. The basal metabolism is often increased in erythremia. The increase is believed to be affiliated with the augmented activity of blood formation, as it is in myelogenous leukemia.

6. The development of marked anemia in erythremia, as in leukemia, is dependent upon a disorderly proliferation of the myeloid tissue.

7. In erythremia, some increase in the output of urobilin is the rule and commonly microcytes occur in the blood. These findings, as well as perhaps alterations of the serum and red cell fragility, suggest that increased blood destruction takes place, though post-mortem studies seldom reveal signs of such a process.

8. Some of the fluctuations in the level of the red cells and hemoglobin probably depend upon variations in the balance between blood destruction and blood formation.

9. The influence of the polycythemic process on the red corpuscles is evidenced by the deportment of these cells when placed in hypotonic sodium chloride solution and in hypotonic blood serum.



These tests show the abnormalities indicated below, but do not give necessarily parallel results.

- (a) A lengthening of the resistance range is often observed.
- (b) An increased, normal or decreased initial hemolysis (point of minimal resistance) may occur.
- (c) Complete hemolysis (point of maximal resistance) never occurs in more concentrated solutions than normal. It often takes place in much less concentrated solutions than normal.
- (d) Patients' cells in dilutions of their own or normal serum may yield an abnormally long resistance span and may break up in a dilution of an equivalent of a stronger concentration of sodium chloride than normal.
- (e) Normal cells may hemolyze in dilutions of patients' serum more readily than in their own. The resistance range in either serum is less than that of erythremic cells.

Hence the erythremic serum may exert a hemolytic influence on red corpuscles; in a case of erythremia, some of the cells may be more vulnerable than normal and others distinctly less so.

10. It is suggested that a lengthened resistance span in fragility tests is due to cells of a greater age variety than normal; that an increase of resistance, especially the maximal resistance, is dependent upon an increase of some form of immature cells; and that decrease of minimal resistance is indicative of some hemocidal influence on the cells, or perhaps due to a relatively large number of old or pathological cells.

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## STUDIES OF CAPILLARIES AND BLOOD VOLUME IN POLYCYTHEMIA VERA.\*

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THE study of nail-fold capillaries by Lombard's method is of particular interest in diseases in which one would anticipate changes in the morphology and function of the capillary loops. Weiss, Jürgenson, Magnus, Boas, Brown and others have published

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observations of variations in the capillaries of the skin in certain diseases. Freedländer and Lenhart have observed stasis with dilatation of the arterial and venous limbs of the capillaries in cases of traumatic and surgical shock. These observations agree with our knowledge of the role of the capillary bed in shock and shock-like states in which there is low plasma volume. On the other hand, in conditions in which there is an increased blood volume, one would also expect morphological changes in the capillary bed.

Polycythemia vera is characterized by a definite increase in the cell volume and in the total blood volume. In this condition, the nail-fold capillaries are studied with exceptional ease, for the capillaries are, of course, visible because of their blood content. An increase of the total blood volume and the unit volume of erythrocytes would accentuate the visibility of the capillary loops.

The morphology of the "normal" nail-fold capillary has not yet been accurately established. However, a sufficient number of observations have been made on supposedly normal persons to enable us to say that in certain diseases, the variations as observed in the nail-fold capillaries differ in many respects from the "probable normal" type.

Krogh has shown that the number of actively functioning capillaries is less in the resting than in the active muscle, but that in normal persons the nail-fold capillaries differ from the muscle capillaries in this respect, inasmuch as they maintain a relative constancy of form and number. The caliber of the capillaries changes slightly in response to certain stimuli, such as changes of temperature, mechanical irritation, and according to Hagen, also in relationship to time of day, metabolic disturbances and the menstrual periods. Distinct differences have been noted in the blood flow and the color of the capillaries, in large groups of normal persons during the summer and winter months. On the other hand distinct changes in contour and shape, other than in caliber, have not been observed in nail-fold capillaries when examined at intervals over periods of weeks and months, or under various kinds of stimulation. In certain cardiovascular diseases many loops are seen in which there is a sudden arrest of the blood flow from the arteriolar entrance, with consequent disappearance of the loop for periods of from one to ten seconds. When the flow is resumed, it is seen that the original contour of the loop has been preserved. In acrocyanosis and Raynaud's disease arrest of the capillary flow is observed during the cyanotic phases. In shock complete stasis has been seen.

**"Normal" Capillaries.** The so-called normal nail-fold capillary is shown in Fig. 1. It consists of two portions, a venous and an arterial segment. The so-called connecting limb is a part of the venous limb. The average length of the arterial segment is 0.15

mm. with an approximate average diameter slightly less than 0.01 mm., which increases slightly towards the venous segment. These measurements were made with a modification of the ordinary eye piece micrometer and are consequently not absolute.\* The connecting limb averages 0.034 mm. in length and has an approximate diameter of 0.01 to 0.02 mm. The venous limb is longer than the arterial, averaging 0.18 mm. in length with an approximate diameter of 0.015 to 0.02 mm. The average length of the entire loop is 0.364 mm. These measurements are the averages for

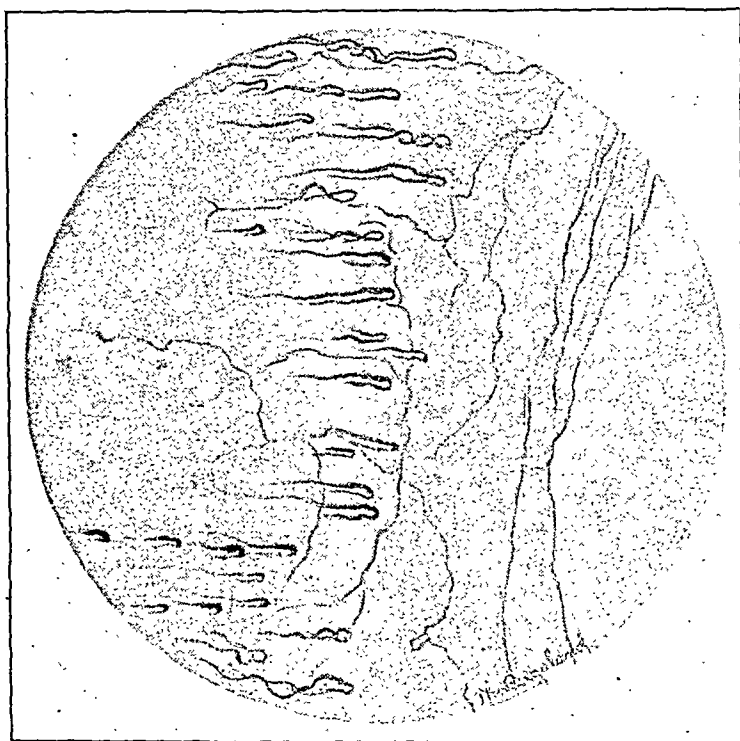


FIG. 1.—Normal capillaries. Scale 1 cm. in length, smallest division 0.01 mm. Usual appearance of nail-fold capillaries as seen in normal subjects. The venous limb is longer and broader than the arterial. The capillary flow is rapid so that the individual erythrocytes cannot be distinguished.

27 persons classified as normals, studied under fairly constant conditions with respect to position, level of hand, and temperature.

The commonest form of normal is the hairpin type. There is, however, considerable variation in the shape and size of the normal loop. Short and broad, long and slender, and tortuous types are often seen. In each person there is usually a predominating type of normal capillary which constitutes the majority of loops for each field. In a large group of supposedly normal persons of

\* We are at present working on a more accurate instrument for measuring changes in loops so that the most minute variations of caliber can be followed.

different ages, atypical or bizarre types of capillary loops are seen, but these are not as common in normal as in certain pathological conditions. The establishment, if possible, of the range of variability in normal persons is essential to further investigation.

The capillary flow can be easily studied with a magnification of 50 diameters. Either a single or stereoscopic lens may be used. The rate of flow is measured and studied in relation to its character. Retardation, intermittency, jerkiness and to-and-fro movements of the blood column are particularly noted. Variations in the rate of flow are common, depending on the temperature and the position of the hand and probably other factors. The rate of flow seems to vary within certain limits which are subject to measurement. Since there is a wide range of rate of capillary flow in normal persons, we have noted only marked changes as having a probable significance. Markedly low rates are often found in cases of neurasthenia, acrocyanosis, shock and shock-like states, and in severe cases of cardiorenal-vascular disease. In the normal group the average rate of flow in individual loops was found to be approximately 1.01 mm. each second. This average rate is somewhat less than it should be as the fastest rates of flow could not be measured with accuracy. The rate as given represents the minimal normal rate of at least six different loops with at least three estimations of each loop. The conditions as regards position of hand, and room temperature, were kept as nearly equable as possible. In the study of the velocity it is important to note whether there is a uniform flow in the majority of loops, or whether there is a marked variation of flow in different loops. In patients with severe cardiorenal-vascular disease very marked sudden changes of velocity are often noted, varying from complete stasis in many loops, to extremely rapid velocity; complete disappearance of the loops with obliteration of blood column at the arteriolar entrance is frequently observed. This behavior of the capillary suggests a spasm of the arteriole and should be studied further.

**Nail-fold Capillaries in Polycythemia.** The appearance of the nail-fold capillaries has been studied in a group of patients with polycythemia, which included 5 patients with true polycythemia, 1 with polycythemia associated with congenital heart disease, and 1 patient in whom the blood and clinical studies would permit of only a provisional diagnosis of polycythemia vera. This is classified as "probably" polycythemia.

In Table I are the measurements and observations of the nail-fold capillaries in these cases (Figs. 2, 3 and 4). It will be noted that the nail-fold capillaries show definite engorgement of either one or both segments in the cases of polycythemia vera, although this is not uniformly present in all loops. Occasionally quite normal types are seen. The engorgement is more evident on the venous side. In all but 1 patient, a case of probable polycythemia,

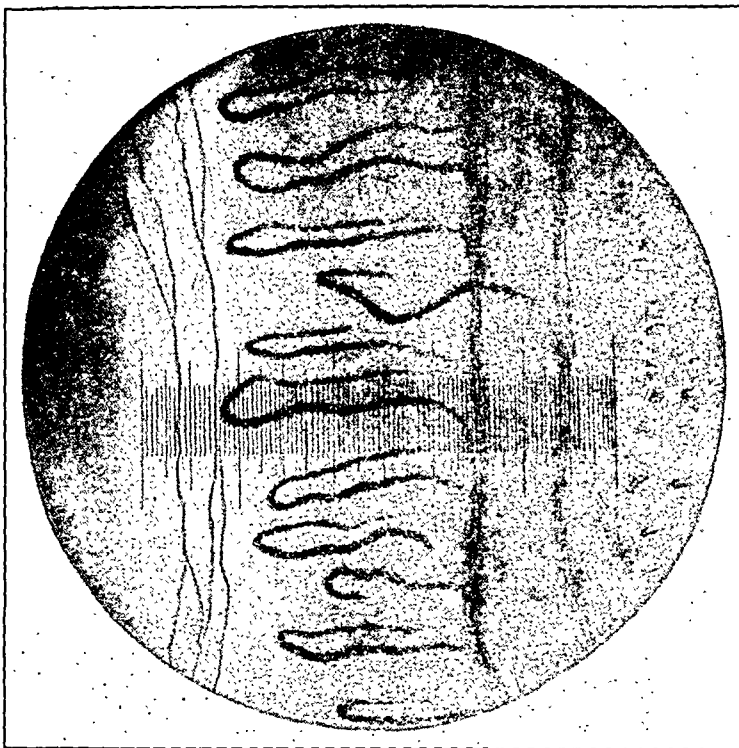


FIG. 2 (Case A406484).—Scale 1 cm. in length, smallest division 0.01 mm. Sketch of nail-fold capillaries in a case of polycythemia secondary to congenital heart disease. The loops are increased in length with almost equal engorgement of both the venous and arterial segments. The collecting venules also show marked engorgement.

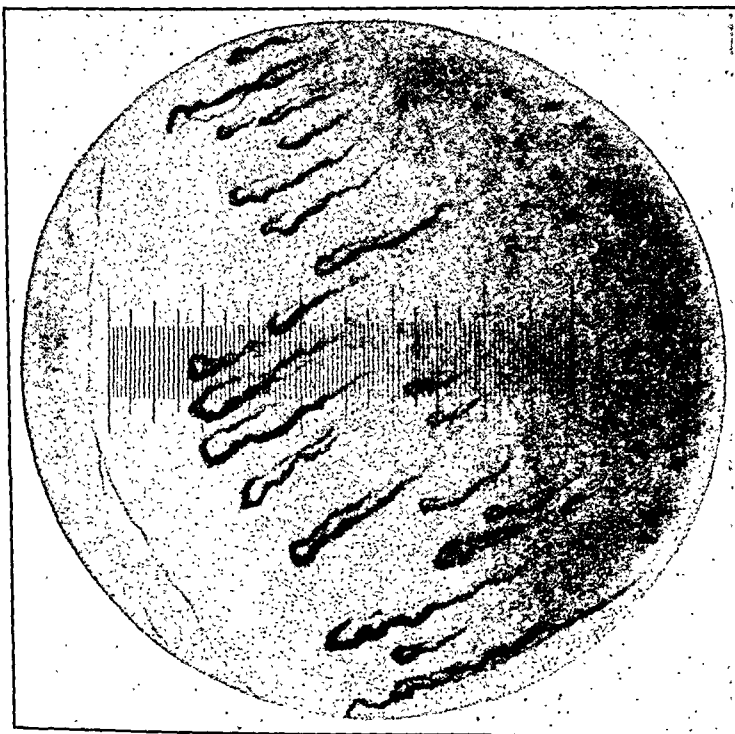


FIG. 3 (Case A405531).—Scale 1 cm. in length, smallest division 0.01 mm. Sketch of nail-fold capillaries in a case of polycythemia vera. Marked engorgement and slight tortuosity of the venous and arterial limbs. The total lengths of the capillary loops are increased. Note the thin arterial segment.

TABLE I.—STUDIES OF CAPILLARIES OF THE NAIL-FOLD IN POLYCYTHEMIA.

Case.	Fingers examined.	Average loops for each mm.	Length of arterial limb, mm.				Length of venous limb, mm.				Length of connecting limb, mm.	Average length of capillaries, mm.	Rate of flow each second in two different capillaries, mm.	Observations on capillary flow.	Description of capillaries.
			Maximum.	Minimum.	Average.	Diameter.	Maximum.	Minimum.	Average.	Diameter.					
1 A404580	3	8	0.40	0.10	0.15	0.01	0.80	0.20	0.48	0.02	0.04	0.67	0.3, 0.7, 0.8, 0.14, 0.20	Stream uniformly rapid, visible as a mass of moving cells	Long straight types of loops with broad connecting and venous limbs. First appearance resting capillaries but later contain rapidly moving homogenous mass of cells. Collecting venules visible, distended.
2 A405531	4	9	0.45	0.10	0.24	0.02	0.45	0.20	0.27	0.03	0.05	0.56	0.7, 0.10, 0.12, 0.3, 0.14	Moderately slow flowing stream. Mass red cells many with fairly uniform speed	Many long distended types of loops. Many huge loops seen. Venous limb showed the greater engorgement.
3 A396804	Second right hand Second left hand	9 Clubbing of distal phalangeal joints ..	0.30 0.40	0.20 0.30	0.23 0.39	0.01 0.016	0.60 0.65	0.40 0.40	0.43 0.56	0.02 0.03	0.04 0.03	0.70 0.98	Stream too rapid for accurate measurement	Uniformly rapid flow. No disappearance of loops	Long regular types of loops. Engorgement not marked. Arterial limb relatively fine as compared to venous limb. Collecting venules visible with moderate engorgement. Frequent anastomoses. Large dilated capillary loops both arterial and venous limbs engorged. Venous limbs appear huge.
4 A406484	3	7	0.40	0.20	0.28	0.025	0.60	0.25	0.51	0.04	0.045	0.835	0.40, 0.35, 0.20, 0.28 0.50	Fairly rapid flow. Uniform speed	

5 A414076	3	9	0.14	0.07	0.092	....	0.28	0.11	0.17	....	0.042	0.30	Stream moderately slow, uniform rate	.....	Moderately dilated limbs. Tortuosity frequent relatively fine arterial limb. Venous portion dilated with sharp transition into more narrow arterial portions seen. Capillaries not distended to degree as noted in Cases 1, 2, and 3.
6 A416727	3	..	0.05 0.07	0.30 0.42	0.16 0.224	0.01 — 0.014	0.10 0.14	0.35 0.49	0.24 0.336	0.02+ 0.028	0.024 0.034	..... 0.594	0.048, 0.05, 0.01, 0.03, 0.039	In normal appearing capillaries flow is rapid. In distended loops flow is slow, barely moving. No complete stasis observed	Tortuosity present in majority of loops. One-third of total number of loops show huge distended forms. Engorgement is shown mostly in venous and connecting limbs. Arterial segment is fine. Thread-like type such as frequently observed in patients of this age.
7 A410617	3	7	0.14	0.07	0.10	0.01 —	0.21	0.07	0.145	0.01	0.036	0.281	Stream too rapid for accurate measurement* 0.14, 0.15 0.21, 0.24 1.01	Rapid, uniform flow	Hairpin type, short loops. No engorged or dilated types seen. Fairly normal field.
Group of 27 normal persons aged 20-50 years	3	9	....	....	0.15	0.01	....	....	0.18	0.018	0.034	0.368			

\* Minimal velocity.



the total length of the loop is greater than in normals of like age. The caliber of the venous limb is distinctly widened and occasionally huge dilated limbs are seen; they are suggestive of the varicose changes observed in peripheral veins. Similarly, the collecting venules are often engorged to twice or more their normal diameter. The arterial limb of the loop is not enlarged to the same extent as the venous. In the patient with "probable" polycythemia, engorgement was not observed.

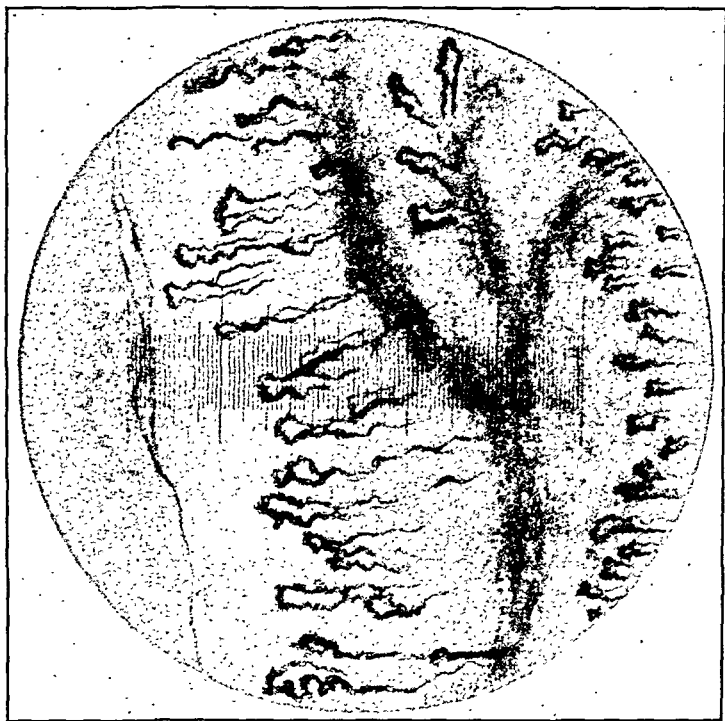


FIG. 4 (Case A404580).—Scale 1 cm. in length, smallest division 0.01 mm. Sketch of nail-fold capillaries in a case of polycythemia vera. Some of the capillaries show engorgement of the entire loop. There is considerable tortuosity of arterial and venous limbs. The collecting venules are markedly engorged.

In 2 cases, many of the arterial segments were of the fine contracted type which is commonly seen with increasing age, in cases of arteriosclerosis and of hypertension. This contraction of the arterial segment gives a sharp demarcation point between the arterial and venous limbs (Fig. 3). Older patients showed a tortuosity which probably had no relationship to the polycythemic condition. The contraction of the arterial segment and the tortuosity seemed to be related to age rather than to excessive blood volume. In the younger patients, the capillaries maintained the usual "hairpin" shape. In Case IV, polycythemia associated with congenital heart disease (Fig. 2), the arterial limb participated in the engorgement practically to the same degree as the venous

portion. This gave a uniform dilated type of capillary loop which was entirely different from those in the other patients.

The velocity of the capillary flow is distinctly and uniformly decreased. The movement of the erythrocytes is *en masse* rather than in the rapid single-file manner usually observed in normals. The cells move as a densely packed mass, with a twisting onward motion. Occasionally the onward flow from the arterial segment will heap up in the already distended venous limb. Complete stasis was not observed except when the hand was exposed to lower temperatures. As will be seen in Table I, the velocity rates for the capillaries of the same individual show a rather uniform slowing. Sudden and uneven changes in speed were not noted.

**Blood Studies in Polycythemia.** The total blood and plasma volumes were determined by the method of Keith, Rowntree and Geraghty. According to these workers, the total circulating blood volume in normal persons varies from 78.5 to 97 cc for each kilogram of body weight. The ratio of total blood volume to body weight varies from 1:13 to 1:10.5, the average being 1:11.4. The plasma volume varies from 42 to 56 cc for each kilogram of body weight. The ratio of plasma volume to body weight varies from 1:23 to 1:17 with the average of 1:19.4. As will be seen in Table II, the patients in this report showed marked increases in the total circulating blood volume and only slightly increased plasma volumes. The total number of erythrocytes was high and the cell-plasma ratio as shown by the hematocrit studies was greatly in favor of the cells. In determining hematocrit values in these studies, dry sodium oxalate (10 mg. to 10 cc of blood) and defibrinated blood were both used in each estimation. The difficulty of obtaining complete sedimentation of blood with a viscosity as great as that obtained in polycythemia must be taken into consideration. The concentration of cells for each unit volume was variable, but an excessively high erythrocyte count was observed only in 1 patient. The erythrocyte count bore no direct relationship to the blood volume, as the patients with the largest blood volume showed only a moderate increase of cells for each cubic millimeter.

**Discussion.** The vascular changes in polycythemia vera are chiefly concerned with (1) readjustment of the vascular bed to the augmented blood volume; (2) changes in the vessel walls, probably due to strain, metabolic disturbances and various other factors; (3) vascular plugging, probably due to thrombotic processes as a result of increased viscosity and changes in vessel wall and the coagulation factors of the blood; and (4) changes in the erythro-genic tissue. So far as this study is concerned, the findings apply chiefly to a consideration of readjustment of the vascular bed.

The accommodation of the bloodvessels to the increased blood volume of polycythemia probably occurs first in the large veins

TABLE II.—BLOOD VALUES.

Case.	Age, sex.	Diagnosis.	Weight, kg.	Plasma.		Ratio to body weight.	Hematocrit.		Total blood.			Erythro- cytes, per cent.	Hemo- globin, Haldane- Palmer, per cent.
				Volume, cc.	Ce for each kg.		Erythro- cytes, per cent.	Plasma, per cent.	Volume, cc.	Ce for each kg.	Ratio to body weight.		
A404580	60 M.	Polycythemia vera	72	4641	64	1-15	57	43	10,830	150	1-6.6	5.77	115
A405531	50 M.	Polycythemia vera	63	4261	67	1-14.8	70	30	14,203*	224	1-4.4	6.55	145
A390804	55 M.	Polycythemia vera	62	2882	46	1-21	66	33	8,733	140	1-7	7.14	166
A414676	47 M.	Polycythemia vera	62	3955	64	1-15	65	35	11,300	182	1-5.5	8.93	145
A416727	53 M.	Polycythemia vera	59	4571	77	1-13	52	48	9,523	161	1-4.8	5.82	158
A406484	30 M.	Polycythemia vera? with con- genital heart disease?	69	4500	65	1-15	60	40	11,250	163	1-6	6.88	136
A410017	25 M.	Probably early polycythemia	60	3705	63	1-16	52	48	7,843	130	1-7.7	5.75	117

\* Probably too high.

and in the more vascular organs, especially the spleen. As the condition progresses the smaller veins participate in the engorgement. This can be observed in the peripheral and the retinal veins. As the condition becomes more advanced the capillaries of the skin and of the mucous membranes share in the engorgement, which is macroscopically more apparent in the latter tissue. As will be observed, the venous portion of the capillary loops shows a much greater degree of distention than the arterial portion. The arterial limb may also participate, as may be seen in Fig. 2. The clinical features of the disease seem to agree with this conception of the vascular adjustment. The milder cases may show only slight erythrosis of the skin and mucous membranes.<sup>12</sup> With greater increases in blood volume, congestion and erythrosis\* of these tissues become evident. Probably many of the symptoms of polycythemia are not produced until the engorgement has progressed to the smallest vessels. The more serious vascular accidents occurring in the disease are late manifestations.

The differences in the degree of engorgement of the arterial and venous limbs often allow a clean-cut demarcation of these segments. The dividing line is sharp, that is a sudden transition from a finer segment to a distended limb, is seen on the distal portion of the arterial limb (Fig. 3). The connecting limb seems to be a part of the venous segment, as these portions participate in the engorgement in like degree. This difference of distention or dilatation of the venous and arterial limbs suggests either an essential difference in endothelial tissue, or a different vasomotor control. The differences in the appearance of the capillary seem to bear no relationship to the blood-pressure estimations. In Case I (Fig. 2) this distinction between the arterial and venous portions is not seen. Both portions seem to be uniformly engorged. This case was not a true polycythemia, but possibly polycythemia secondary, due to congenital heart disease. It could be assumed that these capillaries had been subjected to engorgement early in life with definite changes in both arterial and venous portions.

The retardation and the character of the flow in the capillaries are consistent with the increase in viscosity which is present. One can visualize the difficulty with which free capillary circulation is maintained. The mass and the viscosity of the circulating

\* Lundsgaard has shown in a case of polycythemia that the difference between the oxygen saturation and oxygen content of the venous blood was not increased. In other words the percentage of oxygen unsaturation was normal. Therefore, cyanosis was not present. The term erythrosis was suggested to designate the skin color of polycythemia. Visualization of the capillary blood shows the cells to have bright red color at room temperatures of 20° to 30° C. Short exposures to cold produce further slowing or complete stasis of the capillary stream with an evident bluish tinge to the corpuscles. The changes in color are much more striking than in normals, because of larger cell mass. It is quite probable that varying degrees of cyanosis are present at different times, even though fundamentally polycythemia is correctly regarded as an erythrosis.

fluid tend to create a slow rate of flow in the minute capillary loops. This slow rate of flow may be compensatory, in view of the abnormally high oxygen content. Moreover the distention may facilitate a freer circulation, and when distention ceases, vascular difficulties may arise. It is evident that a larger amount of blood than normal is passing through the capillary bed and a greater amount of oxygen is available for tissue needs for each given unit of tissue. A slower circulation rate would be adequate; conversely in anemia an increased rate of flow is present. Fahr and Ronzone have shown that, in the skin capillaries of a case of severe anemia, the contracted forms are present which are probably compensatory in maintaining an increased circulatory rate. In polycythemia we would not expect cardiac hypertrophy since the minute volume output of the heart should theoretically be small.

**Protocols.** CASE I (A404580).—J. R., a man, aged sixty years, had always been full-blooded, more noticeably so during the last year; splenomegaly had been noted one year before. He had complained of fatigue, loss of weight, polydipsia, and polyuria for six months. Special examinations revealed glycosuria 1.4 per cent (5.16 gm.), blood sugar 0.27 per cent, hemoglobin, acid hematin 115 per cent, Palmer 115 per cent, erythrocytes 5,770,000, total blood volume 150 cc for each kilogram of body weight, and hematocrit erythrocyte volume 57 per cent.

CASE II (A405531).—F. S., a man, aged fifty years, had been markedly plethoric for several years, and the more so during the last year. The patient complained of headache and dizziness. There was a moderate degree of splenomegaly, and engorgement of the retinal veins. Special examinations revealed hemoglobin, acid hematin 140 per cent, Palmer 145 per cent, erythrocytes 6,550,000, total blood volume 224 cc for each kilogram of body weight, and hematocrit erythrocyte volume 70 per cent. Thrombosis of a vein in the left arm occurred while under observation.

CASE III (A396804).—W. W. T., a man, aged fifty-five years, had had definite symptoms for two and one-half years. He complained of dizziness, and paresthesia, swelling and congestion of the left hand. The hands and mucous membranes were definitely purplish red and the veins were full. Roentgen-ray examination of the arm was negative for calcified vessels. Special examinations revealed hemoglobin, acid hematin 155 per cent, Palmer 166 per cent, erythrocytes 7,140,000, total blood volume 140 cc for each kilogram of body weight, and hematocrit erythrocyte volume 66 per cent.

CASE IV (A414676).—J. M., a man, aged forty-seven years, had had swelling in both legs, and attacks of congestion and an aching pain for four years. These attacks occurred every two or three months and lasted for two or three weeks. A moderate degree of splenomegaly was noted. Roentgen-ray examination of the legs was negative for any evidence of sclerosis of the vessels. Special examinations revealed hemoglobin, acid hematin 136 per cent, Palmer 145 per cent, total blood volume 182 cc for each kilogram of body weight, hematocrit erythrocyte volume 65 per cent and viscosity 11.2.

CASE V (A416727).—J. C. R., a man, aged fifty-three years, had had epistaxis for many years, and during the last year attacks of hematuria. The urological examination revealed evidence of a left renal tumor. The patient, however, had the appearance of a true polycythemic. Special examinations revealed hemoglobin, acid hematin 140 per cent, Palmer 158 per cent, erythrocytes 5,820,000, total blood volume 161 cc for each kilogram of body weight, hematocrit erythrocyte volume 52 per cent, and viscosity 7.8. Following a severe hematuria of three days' duration, the hemoglobin dropped to 137 per cent Palmer, and the total blood volume to 127 cc for each kilogram of body weight. The skin capillaries revealed a definite diminution in size.

CASE VI (A406484). A. M. C., a man, aged thirty years, who had always been full blooded, had been told six months before that he had polycythemia and splenomegaly. He had petit mal for seven years and grand mal for two years. The spleen was very large. Clubbing of the toes and fingers was present and there was clinical evidence of congenital heart disease. Special examinations revealed hemoglobin, acid hematin 136 per cent, Palmer 136 per cent, erythrocytes 6,880,000, total blood volume 163 cc for each kilogram of body weight, and hematocrit erythrocyte volume 60 per cent.

CASE VII (A410617).—W. E. B., a man, aged twenty-five years, had complained of headache, vertigo, insomnia, and restlessness for six months. His color was suggestive of polycythemia, but the diagnosis was somewhat questionable. Special examinations revealed hemoglobin, acid hematin 115 per cent, Palmer 117 per cent, erythrocytes 5,750,000, total blood volume 130 cc for each kilogram of body weight, hematocrit erythrocyte volume 52 per cent, and viscosity 7.8.

**Conclusions.** 1. Seven cases of polycythemia vera were studied. In six of these in which a definite diagnosis of polycythemia vera

could be made, the nail-fold capillaries revealed marked engorgement of either one or both capillary limbs. In one case in which the diagnosis was less definite, only slight engorgement was observed. The venous side of the capillary loop was usually more markedly distended than the arterial.

2. In twenty-seven supposedly normal controls, the average total length of the capillary loops was 0.368 mm.; in cases of polycythemia vera 0.602 mm.

3. The measurements of velocity of flow indicated a very definite decreased rate of flow in polycythemia vera.

4. Estimation of the blood volumes in these patients revealed marked increases of cell volume and total blood volume.

5. The relationship of these observations to certain features of the disease is considered.

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## THE CURATIVE TREATMENT BY SPLENECTOMY OF CHRONIC THROMBOCYTOPENIC PURPURA HEMORRHAGICA.\*

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THE theme of this paper is the control, by an apparently curative measure, of hemorrhage in one variety of the heterogeneous group of the affections generally classified as belonging to the hemorrhagic diseases, whose foundation was believed by ancient and less modern internists and pathologists even as late as the beginning of this century to be dependent upon a hemorrhagic diathesis. The term diathesis is here used in its broad sense as indicating an individual tendency, hereditary or acquired; in this instance, a tendency to bleeding, or rather for blood to escape from its containing vessels, chiefly the capillaries. Just as gout was conceived as a disease, essentially depending upon a specific diathesis now known as affecting protein metabolism, so were these cases of bleeding considered to be due to some inherent analogous defect; but with the group of bleeders perhaps used more significantly, because, for instance, in one of the varieties which is known as hemophilia, a patient during the time in which no bleeding occurs exhibits not only no manifestation of his individual tendency to bleed, but seems to be perfectly well.

It was just stated that we wanted to present a seemingly curative measure against bleeding in a special variety of the class known as purpura hemorrhagica, or under the eponym *morbus maculosus werlhofii*, which Werlhof<sup>1</sup> separated from the other varieties of hemorrhagic diseases in 1731. Werlhof's disease is an affection proceeding through an acute, a subacute or a chronic course, and having definite characteristics which separate it from the other members of the general group. The subacute and chronic variety in the past have been attended frequently by fatal results, and it is this variety in which we shall show that by a surgical procedure death may be averted and the disease apparently arrested.

It is known that the escape of blood from its containing vessels may accompany many diseases, either as a common manifestation of them in their course or as an unusual incident. Briefly to

\* Presented at the stated general meeting of the New York Academy of Medicine, February 15, 1923.



bring these diseases to the reader's attention, may we present only the prominent examples of the varied types, omitting the detailed mention of all others. Bear in mind, however, that in all of them the pathogenic factors are either a perverted function of the cells of the capillaries, due to some pathological state in them, or to a change in the blood itself, or to a disturbance or a perverted function or to disease of the hemopoietic system, in one or more of its components—bone marrow, spleen or liver. In all varieties, the manifestation of this hemorrhagic tendency appears clinically as hemorrhagic spots in the skin (when very small, called petechial; when larger, purpuric spots; and when very large, called ecchymoses), and bleeding from the mucous surfaces, commonly from the nose, uterus, the stomach and the intestines, more rarely from the kidneys. These symptoms may be combined or appear singly.

Inasmuch as hemorrhages into the tissues commonly occur as the result of changes in the blood itself, one of these changes most commonly present being a diminution in number of the blood platelets, a thrombocytopenia, the purpuras may be classified as those with thrombocytopenia and those without. The latter very probably depend upon other fundamental changes either in the capillaries or in other elements of the blood.

A. In the first group, the thrombocytopenic, belong:

1. The bacterial infections, such as streptococcus, staphylococcus, pneumococcus, meningococcus.
  - (a) Infections in which as yet no bacteria have been found, *e. g.*, smallpox, measles.
2. Diseases of the hemopoietic organs—leukemia, aplastic anemia, pernicious anemia, splenomegalic cirrhoses, including the Banti syndrome and Gaucher's disease.
3. Poisons:
  - (a) Biochemical, *e. g.*, heterologous sera, snake venom.
  - (b) Organic, *e. g.*, turpentine, balsams, quinine, belladonna, benzol.
  - (c) Inorganic—metallic poisons, such as arsenic and iodine.
4. Nutritive disturbances, such as follow deprivation of vitamins, *e. g.*, rickets. It is peculiar that scurvy, which is also a vitamin-deficiency disease, in which hemorrhages are very pronounced, does not show a blood platelet diminution.
5. Senile purpura.

B. The non-thrombocytopenic group; the causes for the hemorrhages in this group are various, residing in the capillaries and in the other constituents of blood.

1. Hemophilia.
2. Cholemia.

3. Arthritis, such as Schönlein's disease or peliosis rheumatica.
4. Henoch's purpura.
5. Hypertensive vascular states, *e. g.*, arteriosclerotic purpura usually associated with nitrogen retention and other evidence of disturbed renal function.
6. Congenital; sometimes inherited vulnerability of the capillaries, in which instances ecchymosis of the skin occurs with the slightest bruise or trauma and in which cases petechiæ arise in the lower extremities on prolonged standing (static purpura). In such cases the application of a tourniquet or of an inflated cuff of a blood-pressure apparatus may call forth these petechiæ when applied to an upper extremity
7. Some diseases of the nervous system, including the uncommon stigmata such as blood-sweating and purpuric spots, occurring in hysteria.
8. Evolutional changes occurring in women immediately before and during the menopause.

However, it is to none of these that we shall give attention, but to a definite affection commonly diagnosed as belonging to the hemorrhagic diseases, and specifically known as pseudohemophilia, purpura hemorrhagica or the macular disease of Werlhof. It will be wise, before we relegate the affection to a distinct category, to give in clinical terms the characters of the disease so that the reader shall know with what variety of the purpuras we are dealing.

It must here be mentioned that none of the agents usually employed as hemostatics can be relied upon to stop bleeding in this disease, which, unless Nature interfered with her as yet unknown processes, causes the death of the patient very frequently.

First, this variety is not hereditary; patients with bleeding ancestry do not belong to the group. It occurs in youth, even in early childhood, starting with petechiæ, purpuric and ecchymotic spots scattered in the skin of the entire body; petechiæ also occur in the mucosa of the buccal surface, of the palate and pharynx. This disease is commonly accompanied by hemorrhage from the gums, from the nose, less frequently from the stomach, intestines and kidneys, and in the case of girls sometimes by menorrhagia. The vulnerability of the capillary vessels is a feature; these individuals show ecchymoses in the skin on the slightest trauma, and if the static resistance test be applied (capillary resistance test, Hess<sup>2</sup>) by tourniquet to an upper extremity, it will be followed after five minutes of application by a shower of petechiæ in the skin of the extremity to which such a test was applied. The hemorrhages from the nose and gums may last many days and then cease, to be resumed after an interval, thus pursuing an intermittent course with frequent recurrences until the repeated losses

of blood reduce the patient to such an excessively weakened state that he becomes absolutely incapacitated, unable even to sit up, and makes of him a bedridden helpless being. On the other hand, the attack may be continuous, lasting weeks or even months without intermissions, the constant bleeding, which cannot be permanently checked, exsanguinating the poor sufferer until death puts an end to him and his disease.

Again, an attack may occur as an acute one *at any age*, even as late as the sixth decade of life (of which we have at present an example, a female, aged fifty-six years, in the wards at Mt. Sinai Hospital), having identical clinical characters; it may run a fatal course in two or three days, or after one, two or three weeks, or it may disappear as inexplicably as it arose, the patient being restored completely, or it may go over into the subacute or chronic form. In all forms, acute, subacute and chronic, fever may be present, usually, however, most marked in those cases where blood extravasations are large and absorption from blood clots takes place.

In the subacute and chronic cases, the picture is that of a young, ghastly-white, blanched-faced individual, bedridden, with dried blood crusts on the lips, the teeth covered with clotted remnants of blood arising from the bleeding gums, and from the nostrils may be seen extruding hemorrhagic clots from which oozes fluid blood, which trickles down over the lips. The gums in these patients are very spongy, and almost constantly in a state of bleeding; no ulcerative stomatitis occurs. Attempts at stopping the bleeding meet with very little or no success, whether by mechanical agencies, such as a compression tampon in the nares, or agents like other blood, horse serum, calcium salts, thrombogenic solutions of tissue cells, thrombokinas, adrenalin or gelatin, though employed locally or by way of the vascular channels.

An examination of the blood of the patient shows certain characters which individualize this disease and throw some light upon its pathogenesis. First of all, the blood shows a marked diminution or, in rare instances, an entire absence of the blood platelets, which, as is known, normally exist in every human blood and average 250,000 per cm.; the platelets may be reduced so that in rare instances none can be found and in commoner instances numbering a few hundred to 40,000 to 50,000 per cm. Inasmuch as the platelets have been called by that name, also hematoblasts and thrombocytes by different hematologists, this diminution has given the name to this form of purpura hemorrhagica, viz., essential thrombocytopenia or, adjectively, essential thrombocytopenic purpura hemorrhagica, the latter in our opinion being preferable because the name describes its pathogenic and clinical attributes.

We are indebted to Hayem,<sup>3</sup> in France, for calling attention to the isolated observation of Denys,<sup>4</sup> that in a case of purpura,

which the latter had studied, there were few blood platelets to be found in the blood. Hayem made the further observation that it was curious to find that Denys's observation was true in many instances of purpura. It was left to E. Frank,<sup>5</sup> in Germany, to make a more intensive study of these observations and to announce that the diminution of thrombocytes was a constant occurrence in such cases of purpura, and hence he proposed the name of essential thrombopenia for this disease—not a good name, because thrombin is the name given to one of the hypothetical factors which occasions coagulation of the blood, and the disease is not due to any marked disturbance in this process. Hence, Eppinger,<sup>6</sup> suggested the term thrombocytopenia, because the word indicated the characteristic decrease in the number of thrombocytes. Frank believed the disease was a mild type of aplastic anemia.

Another feature of this disease was also detected by Hayem, namely, that when the blood taken from a patient suffering from essential thrombocytopenia is permitted to clot, which it does in the normal time, in a glass tube, the blood clot does not retract from the walls of the tube, as does normal blood, but remains unretracted, filling the entire lumen. A normal blood clot retracts within an hour, soon showing a zone of serum about it, and intervening between the clot and the periphery of the tube's lumen. It is highly probable that the degree of retraction of the clot depends upon the number of blood platelets in the blood which cause a firmer and more fibrinous coagulum than occurs in the clotting process of blood in essential thrombocytopenic purpura hemorrhagica, which Pagniez<sup>7</sup> demonstrated. It should be remembered that the clotting time of blood in this disease is not diminished. This fact at once differentiates this group of bleeders from those suffering with the disease known as hemophilia, because in the latter there is a constant marked factor present, namely, an inherited defect in the clotting factors of the blood, so that clotting is markedly delayed and imperfectly executed, though after clot formation occurs, clot retraction takes place.

Another characteristic of the blood in essential thrombocytopenic purpura is one to which both Hayem and our own countryman, Duke,<sup>8</sup> called attention—the bleeding-time, or the time occupied before capillary bleeding ceases, is greatly prolonged. The normal bleeding-time after a skin puncture consumes one-half to three minutes; in purpura hemorrhagica ten or more minutes may be consumed before such bleeding ceases. It is highly important that clotting-time and bleeding-time be not confused. Bleeding-time is best tested by pricking an ear lobe and noting the time which elapses before the bleeding stops. Of course, the tissue pricked must be left undisturbed, because pressure exerted upon the traumatized spot, or the placing of a foreign body like a wisp of cotton over it will materially shorten the time for bleeding to cease.

No change occurs in the fragility of the red blood cells in this disease.

In other respects the blood shows no demonstrable changes. Of course, the red blood count will vary with the amount of blood lost, the degree of anemia present, and the capacity of the bone marrow to generate new red blood cells. The hemoglobin of the blood is constantly reduced below the normal relationship of red blood cells to hemoglobin, the color index being much below 1, usually 0.5 to 0.6. A hypochromatic type of anemia is, therefore, always present. The myeloid and lymphoid derived cells of the blood show no changes; there is, as a rule, neither leukocytosis nor leukopenia, and the polymorphonuclear cells show their usual proportion to the lymphocytes. The monocytes are commonly increased, sometimes as high as 20 per cent, possibly as the result of an active regeneration, when leukocytosis may also occur. Blood smears show moderate changes in form in the red cells, moderate increase in the number of microcytic forms and very occasionally a few normoblasts. Marked polychromasia, macrocytosis and megaloblasts are lacking.

With the constant loss of blood, the bone marrow may become entirely exhausted on account of its continuous activity in generating new blood cells, and a fully developed aplastic anemia may ensue with a quickly fatal termination.

It should also be noted that the few blood platelets which are present in this disease show many large forms, even two to three times their normal size. Wright's<sup>9</sup> observation may be recalled that blood platelets are formed from the fragmentation of the megakaryocytes of the bone marrow. The megakaryocytes extrude pseudopodia into the reticulo-endothelial channels in the bone marrow, which pseudopodic processes become broken off and are thus retained as blood platelets in the capillaries which are derived from those channels. These are questions for consideration whether in this disease the megakaryocytes are themselves affected by the morbid process and give rise to defective blood platelets, or by abnormal fragmentation occasion those large forms, and also whether their disease may possibly be responsible for their diminished production.

**Pathogenesis and Treatment.** All hematologists who have had any experience with this disease believe that one of the factors of its production is a diseased state of the capillaries. In addition to this, the constant diminution of blood platelets suggests that the condition which produces the thrombocytopenia is another factor.

There are only two ways by which a reduction in blood platelets can be brought about—one either because the megakaryocytes in the bone marrow do not produce a sufficient number, or because, on the other hand, if a sufficient number be produced, the blood platelets are immediately destroyed somewhere in the tissues of

the organism. It is supposed that the destruction of blood platelets occurs normally in the spleen where the other elements of the blood are supposed to be prepared for their katabolism. Hence, one of the explanations given as to the pathogenesis of this form of purpura is that a diseased spleen removes most of the platelets before they are ripe for destruction.

Of recent years, the researches of Eppinger, Frank and Kaznelson<sup>10</sup> have thrown some light upon the relationship of the spleen to the rest of the hemopoietic system. Frank, in a study of aplastic anemia, to which, as we have said, he regarded essential thrombopenia, as he called this disease, to belong, thought that bone marrow was activated to renewed activity by removal of the spleen because he believed that its presence inhibited the function of the bone marrow; for this view certain arguments can be advanced. Therefore, on a purely theoretical consideration, he advised the removal of the spleen in all cases of aplastic anemia.

Kaznelson, on the other hand, believed that this disease was not the result of impaired bone-marrow function, but that the blood platelets were removed from the circulation by a diseased spleen. Kaznelson<sup>11</sup> was thus convinced because he found in the spleen of a case of this disease a large number of blood platelets in the open lymph spaces of that organ. Eppinger so believed because when the spleen was removed from the body blood platelets were increased and were found in the blood in much greater numbers than before removal; he argued if the megakaryocytes of the bone marrow were at fault, removal of the spleen ought not have any influence on ablation of bone marrow megakaryocytic function, but ought rather to increase it.

Kaznelson, in the belief that hemorrhage in these cases was due to the thrombocytopenia and that the thrombocytopenia was caused by a thrombolytic function of the spleen, determined to have the spleen removed from one of these patients, and in 1916 put his determination into execution. The results were immediate and brilliant. He states that bleeding ceased at once, petechiae disappeared, the blood platelets became increased in number to normal limits, bleeding-time became restored to normal and the clotting which thereafter took place was accompanied by clot retraction.

Influenced by his results and by the endorsement of the method by Eppinger, we were led to try the method in two patients, in both of whom a fatal termination was rapidly approaching. Both of these patients were suffering with the chronic intermittent form of the disease; both developed the disease in childhood, one at the fifth, the other at the eleventh year of life; both had been subjected to every known method of treatment for stopping the bleeding; both had been absolutely incapacitated for some years; both showed a most intense anemia, in each the hemoglobin was below 20 and red

blood cells were near the million mark; both had been repeatedly transfused, the girl 10 times, the boy 3 times.\*

The results were, as far as the escape from death is concerned equally brilliant. In both, bleeding has been entirely stopped. Their color has returned. Hemoglobin in the girl is 90, erythrocytes, 5,800,000; in the boy the hemoglobin is 80, erythrocytes, 4,816,000 and are gradually increasing. They are able to walk, where previously they had been bedridden. They now take an interest in life and are no longer consumed by the contemplation of a hopeless invalided state. They can play again and have a real joy in living.

It is wise immediately before operation, in order to avoid the loss of blood which attends the operation, as oozing throughout the operative procedure takes place from all cut and exposed surfaces, to have the patient transfused even though we believe transfusion in these cases is otherwise useless; it is also wise immediately to follow the operation again with a transfusion as a means of overcoming the shock. Those procedures we advised in both of these cases and they were followed.

Bleeding from the mucous surfaces ceases a few minutes after the removal of the spleen, and the bleeding-time at once returns to the normal.

We wish to add a few words as to the effect of the splenectomy upon the subsequent manifestations of the disease: The immediate effects are the cessation of bleeding from the mucous surfaces previously involved, and a rapid increase in the number of blood platelets in the circulation. The increase in the first case was from 6000 platelets to 270,000 per cm.; in the second, from 400 to 60,000. This increase, however, is not permanent, and in a few days begins to fall and the fall continues so that the platelets may come down in number again to very low limits. The bleeding-time becomes immediately markedly reduced; in both the patients, as soon as the spleen was removed it fell to less than three minutes; but after a few days it gradually increased but not to the former limits.

We could find no evidence of clot retraction at any time following the operation, though Kaznelson states it occurs. Since the operation in the girl there has been absolutely no bleeding anywhere demonstrable; in the case of the boy, three short-timed hemorrhages have occurred from the nose, possibly due to old crusts and to pathological changes in the mucosa which the retention of a tightly packed tampon induced. For the last six weeks it has not returned. In both there has been a steady progressive

\* We desire to say here that personally we believe from the experience we have had with this disease, that transfusion is not only useless as a curative measure, but seems to increase the bleeding from the mucous surfaces and the number of purpuric spots in the skin, because fresh ones may be seen almost immediately after such transfusions.

increase in hemoglobin and in the number of red blood cells, and the poikilocytosis, anisocytosis and normoblasts have disappeared in the blood. The white blanched pallor is gone and the color of the face assumes the normal tone.

In the girl the static test has been negative; in the boy, however, it was still slightly positive, and he showed on the skin of the lower extremities pin-point petechiæ upon walking and upon standing until two weeks ago, when they also disappeared.

In both the gums, which throughout the disease had been markedly spongy and sodden, showing a persistent oozing of blood, have absolutely returned to a normal state and are now in close apposition to teeth.

Inasmuch, therefore, as the platelets after operation soon become diminished, and showers of petechiæ may persist, and the clotting is not associated with retraction, it would seem that the explanation of Frank and Kaznelson, that the disease is due to essential thrombocytopenia, must be modified. In both these patients, thrombocytopenia has returned, though hemorrhage, the most important symptom, has ceased. It would appear, therefore, that the removal of the spleen has at least stopped the process of active capillary bleeding. Hence, may one not infer that the presence of the spleen in the body in these cases adds something pathic to the blood which permits the ready escape of the latter from the capillaries, and that its removal permits the capillaries to resume their normal function of keeping their contents within their walls? This pathic something may be manufactured in a disturbed or pathological functioning spleen, possibly a toxin, which may be the cause of the disease and which prevents the endothelial cells of the capillaries from exerting their contractile tonus and tonus function which the experiments of the Danish physiologist, Krogh,<sup>12</sup> have demonstrated. This, together with the more important blood platelet defect which characterizes this disease, seem to be the agencies which are responsible for the hemorrhages which occur.

It is difficult to explain the rapid return to a thrombocytopenic state of the blood after the removal of the spleen, even though at first this state had been arrested. The return of the thrombocytopenia destroys the views previously held—either that the spleen acted as a check on megakaryocytic function, on the one hand, or that it destroyed the thrombocytes, owing to a perverted splenic function, on the other, because this feature of the blood was not permanently changed by the spleen's removal. The return of the patient's blood to the condition of thrombocytopenia within two weeks after the operation would seem to indicate that the explanation of the removal of the platelets by a vicarious function on the part of the remaining members of the reticulo-endothelial system and of newly formed hemolymph glands can find little if any support.



**Conclusion.**—It is not our purpose to generalize from the limited experiences following a small number of similar limited experiences in a few other observers. We feel justified in saying that splenectomy in this disease is a life-saving measure and should as such be employed in all grave cases of chronic thrombocytopenic purpura; it most assuredly saved the lives of these two patients. We may also state that there is considerable evidence to believe that splenectomy is also curative. Kaznelson's first case has had no recurrence of the disease in a period of over five years. An inspection and examination of our two patients will show the tremendous benefit it has produced in a seemingly hopeless condition, a benefit which may subsequently prove to be a permanent cure.\*

It would seem as if this disease was really one involving the reticulo-endothelial system, chiefly that of the spleen, and bone marrow. This view is, perhaps, well shown by the fact that the spleen of the girl was truly splenomegalic in size and weighed 1400 gm. on removal. On microscopical examination, it showed a large increase in the number of reticular cells in the sinuses and throughout the entire organ. In the boy, the spleen, on removal, though considerably larger than normal, weighing 340 gm., was not accompanied by nearly as large an increase in these elements. Both these patients seem to be entirely cured. It may be likely that the larger the amount of reticulo-endothelial structure removed, the better may be the result. Hence, the results of splenectomy may be expected to be much more favorable in those cases attended by very large spleens than in those in which the spleen is smaller.

\* Since the above was written (nearly eight months ago) these patients have been absolutely well; there has been no return of the skin eruption nor of bleeding from the gums nor other visceral hemorrhages. The girl has gained 16 pounds, the boy 22 pounds and he has grown one and a half inches in height. Clot retraction is now present.

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## ADRENAL HEMORRHAGE IN INFANCY.

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THE group of cases included in this paper are to be separated from those cases of adrenal hemorrhage that occur in the still-born or just after birth, and which are now known to be caused by asphyxia. Nor are to be included those cases secondary to manifest sepsis of streptococcic, meningococcic or other bacterial origin; or to burns, definite infections, such as diphtheria, scarlet, tetanus or typhoid; or to trauma, leukemia or hemorrhagic diatheses.

**Case Reports.** CASE I.—Evelyn J., aged eighteen months, Jewish Hospital, No. 50868, was admitted to my service at 7.35 P.M., on August 3, 1918. The family history was of no importance. She had been breast-fed until four months ago, since when she was hand-fed. When ten months old, she suffered from a severe diphtheritic laryngitis which responded readily to 10,000 units of antitoxin. For the last few weeks her bowels had been slightly loose, but without blood. This intestinal condition was unaccompanied by fever or other untoward symptom. Two days before admission she had been taken to the country for a respite from the heat of the city. This necessitated a change of milk. Whether this factor was of any importance in the production of the adrenal apoplexy is a matter for speculation.

On the day before admission the child awoke out of sorts, but there was no fever. In the afternoon she was as bright and cheerful as ever, but during the night became very restless, had high fever and vomited several times. No blood was present either in the vomitus or feces. Cough was absent. A local physician found a temperature of 104° F., and diagnosed pneumonia. A few hours later, the fever reaching 105° F., the parents decided to bring the child to the city for treatment. The distance, over 100 miles, was made by automobile. Due to their haste a collision occurred, but the child did not seem in any way traumatized.

On admission into the hospital five hours later, the following was noted: The temperature was 107.5° F.; respiration, 72 and shallow; pulse, 180 and feeble; nutrition, excellent; an appearance of marked drowsiness and collapse; face moderately cyanosed; anterior fontanelle depressed; pupils equal and reacting to light; no rigidity of neck; no Kernig; all extremities flaccid, tendon reflexes diminished; no Babinski. One large petechial spot on right lower conjunctiva; no bleeding noted from any of the orifices.

The lungs were negative, there were no cardiac murmurs and the abdomen was flaccid without palpable spleen or tenderness. Over the entire body, especially on the face, back and extremities, were scattered purpuric spots about the size of a split pea and of a slaty-blue color. The joints were neither tender nor swollen. A diagnosis of hemorrhage into the adrenals with purpura was made and a fatal prognosis given. The leukocytes numbered 7400; the polynuclears, 76; lymphocytes, 20; monocytes, 4 per cent. The lumbar canal was entered, but no fluid obtained.

The treatment instituted consisted of icebags to the head and axillæ, tepid colonic irrigations, camphor and digalen intramuscularly. The child showed no improvement; took no fluids; Cheyne-Stokes breathing developed; the eyes became fixed; the pulse imperceptible; death occurred at 10.35 P.M., about twenty hours from the onset of the acute symptoms.

Postmortem examination, six hours later, revealed the following positive findings: the body showed marked postmortem lividity. The skin and conjunctiva were as described during life. The brain was moderately congested, ventricles not distended and but little fluid existed in the ventricles or subarachnoid space of brain, accounting for previous dry lumbar tap; culture of this proved sterile. The lungs and heart were negative, and culture of the heart blood proved sterile. The thymus was slightly larger than normal. Two minute petechiæ on the subperitoneal surface of the ileum. No blood in the intestine. Spleen slightly enlarged and soft. There were several enlarged glands in the mesentery of ileum and mesosigmoid. Both adrenals were greatly enlarged, purple and preserving a normal outline. On cut section, both showed diffuse infiltration of the cortex and medulla, with bright red blood clot.

CASE II.—Dorothy B., aged seventeen months, had been breast-fed until twelve months old, and later weaned. She had never been ill before. She awoke at 7 A.M. with a slight cry; her temperature taken by the mother was found to be 103° F. She was languid and vomited. An enema and a dose of castor oil were given and vomiting recurred. When seen by Dr. Salwen, at 2.45 P.M., she was alert, and a few purpuric spots were noted. According to the mother, they had first appeared six hours after the onset of symptoms. She was seen in consultation at 4.30 P.M., and the following noted:

Unconscious; occasional purposeless movements of the extremities were noted. There was no rigidity of the neck. The pupils were widely dilated; the right eye deviated upward and outward. A peculiar pale cyanosis of the face was present. Numerous purpuric spots, non-elevated and irregular in outline, varying in size from a pin-head to that of a dime and covering the chest, abdomen,

back, arms and thighs were noted; there were none below the knees or elbows. Livid cyanosis was present in the areas of skin between the purpuric spots. Over the buttocks and other areas of pressure the skin was ghastly white. The tonsils were hypertrophied, but not inflamed. There were no evidences of bleeding from any of the orifices. The heart-beat, upon auscultation, was counted as 210 and regular and of embryonic type. No radial pulse was elicited. The respirations were 52, with expiratory grunt, and regular. The lungs were negative. The heart revealed no murmurs, and was not enlarged. The abdomen and limbs were flaccid. The liver was palpable one inch below the free border of the ribs. The spleen was not palpable. Kernig was absent. The retinal examination revealed blurred disc outlines, with engorged vessels. Lumbar puncture was performed, but no fluid was obtained. Temperature, 106° F.; child in extremis. A hypodermic injection of 2 minims of adrenalin,  $\frac{1}{1000}$  solution, given. The condition grew worse; respirations ceased, but the heart sounds could still be heard 66 to the minute, then became 112 but still regular, and then ceased about three minutes after cessation of respiration. The diagnosis of adrenal apoplexy was made directly upon obtaining the history and noting the purpura.

Consent for partial autopsy, promptly performed at the patient's home within fifteen minutes after death, the following positive findings are recorded: the spleen was enlarged, measuring  $8 \times 4\frac{1}{2} \times 3$  cm., and surface intensely cyanotic purplish-black; on cut section, prominent Malpighian bodies throughout, and pulp not readily removable. Kidneys measured  $6 \times 3 \times 3$  cm.; cut surface pale; markings distinct. One enlarged mesenteric gland measuring 1 cm., markedly congested, purplish and soft. The liver was enlarged and congested.

A large hemorrhagic sac occupied the site of the left adrenal, leaving only a rim of adrenal tissue, dark red in color at the upper pole. On attempted removal, rupture of the blood sac occurred and about 1 ounce of dark non-coagulated blood was evacuated. The right adrenal was normal in size, but intensely hemorrhagic. Smears of the blood taken a few minutes before exitus showed: Polymorphonuclears, 12; small lymphocytes, 52; large lymphocytes, 25; mononuclears, 8; transitionals, 3 per cent. Cultures made from the spleen, adrenals and heart's blood all proved negative bacteriologically. Microscopical examination of the spleen showed marked increase of the pulp elements with tremendous hypertrophy and increase of the lymphoid elements of the Malpighian bodies. The kidneys showed slight degenerative changes of the renal tubules and slight congestion. The right adrenal showed marked diffuse hemorrhagic infiltration in the cortex and medulla, but no distinct blood clots.

**Discussion.** Cultures of the blood, spleen, purpuric areas of skin and adrenal glands in the cases reported in the literature have usually been sterile. It may be that bacterial toxins or toxins resulting from improper feeding are the causative factors in producing this remarkable lesion. Roux, Yersin, Oppenheim and Loeper have injected various organisms into rabbits, guinea-pigs and pigeons with resulting adrenal hemorrhage.

Brown-Sequard, by completely destroying both adrenal glands, produced death in eight hours in mice, nine hours in rabbits, thirteen hours in guinea-pigs and fourteen hours in cats and dogs. That children usually survive a little longer is probably due to the fact that pathological processes are not as instantaneous or complete as in the laboratory experiment. Brown-Sequard's animals survived about twenty-five hours if only one adrenal was extirpated.

The relationship between the adrenal hemorrhage and the accompanying purpura is as yet unsolved. In purpura hemorrhagica, hemorrhage into the adrenals is unusual. It is, therefore, hardly likely that the purpura and adrenal hemorrhage in this group of cases is dependent upon a marked reduction of blood platelets. Further experimental work along the lines of the effects experimental platelet reduction upon the adrenals is necessary; also, in a study of the platelet count in the clinically suspected cases. Little believed that purpura is to adrenal hemorrhage what pigmentation is to Addison's disease.

The adrenals are the only organs showing important pathological changes. As a rule, both are enlarged, retaining their normal contour, and of a deep purple hue, due to the bleeding within. The entire adrenal substance may be destroyed and present the appearance of a large blood sac. Rarely is the hemorrhage large enough to rupture through into the surrounding tissues. On section, the cortex and medulla are both involved—the latter more so. The amount of bleeding varies from multiple pin-point hemorrhages to complete destruction. Occasionally, only one adrenal may be involved, usually the right, and still a rapid death ensue. That the right adrenal is usually the more extensively damaged may depend upon the greater ease of venous stasis, because of the direct opening of the right adrenal vein into the inferior vena cava and that the right adrenal is readily compressed between the liver and the spine. The adrenal bloodvessels do not, as a rule, show either embolism or thrombosis. The author believes that a toxic action upon the capillary walls of the skin and adrenals is responsible for the diapedesis of blood into the tissues. How much is due to vasodilatation, as a result of the loss of adrenalin supply to the capillaries, must in the future be solved by studies of the sugar and adrenalin content of the blood in these cases.

The skin shows extensive purpura. Marked visceral congestion is usually present. The lungs may show extreme engorge-

ment. The mesenteric glands and Peyer's patches are usually swollen and hyperemic. The brain and meninges are engorged. The spleen is enlarged and hyperemic. Occasionally, a few purpuric spots are to be seen in the submucosa and subserosa of various viscera. The thymus may be markedly enlarged. There are no signs of infection in the throat or cervical glands.

In order to understand the symptomatology, a brief description of the anatomy and functions of the adrenal gland may be in order. The adrenal glands are each composed of a cortex consisting of epithelial cells arranged in three layers and rich in lipoids, and a medulla consisting of longitudinal rows of cells which, because of their capacity to stain deeply with chromium salts, are known as chromaffin cells. The cortex arises from the mesoderm, the medulla is closely related in its development and function with the sympathetic vegetative nervous system and arises from the ectoderm. It is, therefore, not so very remarkable that the skin and adrenal medulla should both be simultaneously involved. The medulla produces a secretion, adrenalin, which stimulates the sympathetic nervous system and so increases the tonus of smooth muscle fiber, elevates the blood-pressure and mobilizes sugar from the liver. That the hemorrhage into the adrenals produces a loss of this function and a marked syndrome of adrenal insufficiency is a plausible hypothesis. The hyperplasia of the lymph glands and follicles of the spleen denote status lymphaticus. It has long been known that status lymphaticus is associated with an insufficiency of the chromaffin system. It is likely that the already insufficient adrenal secretion, if further reduced by the destruction of the cells through hemorrhage, produces the speedy exitus.

The babies whose ages, as a rule, vary from two months to two years, are usually breast-fed and have been previously well nourished, thriving and healthy. The onset is sudden. The infant usually awakens in the early morning hours and is a trifle sick; he lies restless and whining until morning. The first significant symptom may be the screams of abdominal pain, or vomiting, or diarrhea, or one or more convulsions. The diarrhea is rarely severe and usually consists of but one or two loose movements without pus, mucus or blood.

Within a few hours of the onset purpura almost invariably occurs. Cases of unilateral or bilateral adrenal hemorrhage without purpura are reported. Death may have been too soon in these cases for purpura to have developed, or perhaps some aberrant adrenal tissue is left undestroyed. The purpura appears as irregular flat purplish spots or blotches, up to the size of a child's palm, on a background of pale cyanosis. It involves an extensive portion of the body, being most marked upon the trunk, arms, thighs and possibly face. Occasionally numerous petechiæ have been

present. Rarely are hemorrhages from the mucous membranes observed

The infant, concomitantly with the appearance of the purpura, presents all the signs of an alarming illness. Collapse, due to extreme weakness of the heart muscle resulting from its attempts to keep up a circulation in an empty peripheral vascular bed, rapidly develops. The body is hot and the extremities are cold. The pulse is rapid, soft, irregular and small, or not felt. Distant heart tones may be present. The face is gray and later shows an intense cyanotic pallor. The eyes are dull and half open. Meningismus is absent, complete relaxation and depressed fontanelles being present. The temperature is elevated to some extent, varying between 100° and 103° F; it may reach 108° F.

The respirations are usually rapid, shallow, quiet and, occasionally, irregular and of a Cheyne-Stokes character. The nostrils are in motion. The lungs are negative or show coarse rales, particularly at the bases.

Abdominal pain is rare. Tympanites may be present. The abdomen is usually soft and not tender, unless intraperitoneal hemorrhage has occurred. In the latter event, a wrong diagnosis of an acute surgical condition of the abdomen may be made. The child becomes drowsy, inert and finally comatose. Convulsions or fall of temperature occasionally precede death. Death usually occurs within six to forty-eight hours from the onset. I have left out of consideration those cases that are instantaneously fatal.

Treatment should consist of repeated large doses of caffeine, strychnine, camphor, pituitrin, or adrenalin in oil, intramuscularly, with the purpose of stimulating the vasomotor centers and contracting the peripheral bloodvessels. Hypodermoclysis of physiological saline solution containing a very minute amount of adrenalin should be given. As a last resort, repeated intracardiac injections of adrenalin solution should be tried.

In those cases where there is a strong suspicion of a fulminating meningococcic septicemia with hemorrhage into the adrenals, it may be justifiable to give 0.5 cc of antimeningococcic serum hypodermically, and if no reaction occurs to give a full dose of serum intravenously or into the longitudinal sinus, if necessary.

**Summary.** Adrenal hemorrhage in infancy is of more frequent occurrence than hitherto reported, and is unrecognized because of non-familiarity with its clinical picture or failure to obtain autopsies.

In this paper are recorded the clinical feature and autopsy findings of 2 cases observed within a comparatively short period.

An acute illness in a previously healthy child which is rapidly followed by a purpura and collapse should, in the absence of signs pointing to meningococcic infection, be sufficient for the correct diagnosis.

# SOME OBSERVATIONS ON THE PHENOLTETRACHLOR- PHTHALEIN TEST AS A MEANS OF DETERMINING LIVER FUNCTION.\*

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SINCE the publication of the work of Rowntree, Hurvitz and Bloomfield,<sup>1</sup> in 1913, advocating the use of phenoltetrachlorphthalein as a test for liver function, considerable attention has been directed to this test. Inasmuch as the dye was first collected through the feces, many discrepancies were noted as to its determination by various observers; so that Whipple,<sup>2</sup> McLester and Frazier<sup>3</sup> and Kahn and Johnston,<sup>4</sup> report unfavorably concerning it, while Sisson,<sup>5</sup> Chesney, Marshall, and Rowntree,<sup>6</sup> and Krumbhaar,<sup>7</sup> on the other hand, consider it of considerable value as a means of determining liver function.

On account of the great variations in result, McNeil<sup>8</sup> recommended the collection of the dye through the duodenal tube, and Aaron, Beck and Schneider,<sup>9</sup> as well as Piersol<sup>10</sup> have since advocated this method. Following the plan advised by Aaron and his co-workers, we have given 169 single injections of this dye to 93 individuals, utilizing the stable solution recommended by them.

**TECHNIC.** The technic in carrying out the test, is as follows: Immediately before injecting the dye, the duodenal tube being held *in situ*, with a strip of adhesive wrapped around it beyond the third mark and the free end of the adhesive strapped on the cheeks, the patient is given two or three glasses of ice-cold water to drink. In nervous hypersensitive patients, hot water should be introduced very slowly through the duodenal tube. The object of the water is to stimulate the gall-bladder to contract, as well as to relax the sphincter of Oddi and to provide a free flow through the tube. When this flow is established, 1 cc containing 75 mgm. of the disodium salt of the phenoltetrachlorphthalein is diluted with 5 cc of sterile physiological salt solution and injected intravenously. It is better in our experience to detach the needle from the syringe and insert it first into the vein, as the color of the dye makes it difficult to note the return of the blood through the needle. A bit of gauze is held firmly around the needle when it is withdrawn to prevent any return leakage, as the phthalein is extremely irritating to the subcutaneous tissues.

\* Presented at the Meeting of the Association of American Physicians, May, 1923,



Previous to utilizing this method of dilution, considerable irritation of the arm resulting from a leakage of the dye through the vein or the escape of even as small an amount as a drop into the subcutaneous tissues was produced and several instances of thrombosis resulted from the action of the concentrated dye on the walls of the vein at the site of the injection; but since using sterile salt as a diluent, we have not noted a single untoward effect.

The flow from the duodenal tube is allowed to run by gravity into successive porcelain basins, containing 2 cc of a 40 per cent sodium hydrate solution to secure the time of maximum appearance of the dye. If the flow through the tube ceases, the patient should be given more water and in some cases where there is no flow of bile, by the use of the water, 3 cc of a 10 per cent hydrochloric acid solution in 30 cc of water should be injected through the duodenal tube.

Due to the possibilities of error we have not followed the method advocated by Piersol;<sup>10</sup> that is, the estimation of the output of the dye, but have limited our studies to its time appearance, which according to our experience, has been extremely constant.

The usual cause of failure to obtain the dye in a normal individual is due either to not having the duodenal tube in proper position or to the absence of a free return flow of water through the tube.

The tables on pages 521, 522 and 523 illustrate the time of excretion of the dye in normal and pathological cases.

As a result of the study of our 93 cases the following observations are noted.

*Method of Administration.* The dye should only be utilized intravenously; when given subcutaneously once and intramuscularly twice to a normal individual having an excretion time of fifteen minutes, there was no appearance in two hours when the tube was withdrawn. Preceding the administration of the dye by a non-surgical biliary drainage, has apparently no effect on the time of excretion.

*Daily Variation in Normal Individuals.* A reference to the table in which the test was made in 20 normal individuals (in every instance more than once) reveals variations of only a few minutes from day to day in the time of appearance of the dye. A longer variation than this we consider indicates either imperfect technic or some pathological affection.

*Effect of Starvation.* Following a six-day or an eight-day fast in the same patient, the time of excretion was nineteen and seventeen minutes, respectively, indicating that starvation has but little direct influence upon the appearance of the dye.

*Age.* The variations of age of the individuals in our table ranged from thirty-seven months to seventy-two years, but both of these extremes were in pathological cases. The average of the normals reveals practically no variation according to age.

The average rate of excretion of all normal cases is thirteen and eight-tenths minutes,

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
1	1	B.	2- 4-22	21	M.	Achylia gastrica	7 min.	9	Constant.
	2		1-31-22				8	12	
2	3	S.	3-15-22	25	M.	Catarrhal jaundice (subsiding)	8	30	
	4		3-17-22				14	30	Faint.
3	5	S.	3-21-22	38	M.	Chronic cholecystitis	8	14	
	6		5-18-22				12	15	
4	7	F.	3-22-22	55	F.	Paresis (early)	8	11	
5	8	C.	2-20-22	26	..	Typhoid relapse	9	11	
6	9	B.	12-22-21	45	M.	Cholelithiasis, chronic cholecystitis	None in	60 min.	
	10		12-23-21				None in	75 min.	
	11		12-24-21				None in	90 min.	
	12		12-28-21				18	24	
	13		1- 5-22				8	12	
7	14	A.	1-25-22	40	M.	Neurosis	20	25	
	15		2- 3-22				9	15	
8	16	C.	3-23-22	35	M.	Gastric neurosis	9	14	
9	17	G.	1-29-22	65	F.	Chronic cholecystitis, cholangitis and gall-bladder calculi	9 min.	13 min.	
	18		2-15-22				15	16	
10	19	D.	5-10-22	55	F.	Chronic cholecystitis, adhesions and morphinism	10	14	
11	20	D.	4-24-22	15	M.	Acute catarrhal jaundice	10	14	
	21		4-26-22				10	16	
12	22	H.	3- 8-22	28	M.	Psychoneurosis	10	12	
	23		3-10-22				10	16	
13	24	Q.	3- 6-22	58	M.	Psychoneurosis	10	10	
14	25	P.	5- 7-22	38	M.	Malnutrition, visceroptosis, neurosis	10	14	
15	26	S.	4-25-22	55	M.	Arteriosclerosis and myocardial insufficiency	10	15	
16	27	T.	.....	14	M.	Epilepsy, achylia nervosa	11	14	
17	28	K.	3-29-22	35	M.	Cancer of rectum with abdominal metastases	12		Faint.
18	29	H.	5- 5-22	55	M.	Chronic cholecystitis, gastric neurosis	10	14	
	30		5- 7-22				15	6	
	31		5- 9-22				10	14	
	32		5-15-22				15	45	
	33		5-16-22				15	18	
	34		5-20-22				19	22	
	35		5-22-22				20	25	
	36		5-31-22				18		
	37		5-24-22				16	18	
	38		1-11-22	40	M.	Given adrenalin Mx	10	14	
	39	G.	1-15-22	..	..	Syphilis, secondary	11 min.	15	
19	40	B.	3- 3-22	..	..	Post eclampsia	14	20	
20	41	T.	1-11-22	42	M.	Chronic cholecystitis, eczema			
	42		1-17-22				13	13	Faint.
	43		1-14-22				12		
22	44	C.	4-12-22	30	M.	Acute cholecystitis	12	18	
23	45	B.	3-27-22	60	F.	Syphilis of liver	11	12	
	46		5- 8-22				25		
24	47	A.	2- 9-22	35	M.	Cardiac decompensation (Chronic passive congestion. Autopsy)	13	16	
25	48	A.	1-13-22	45	M.	(After operation for stones)	15	18	
	49		1-16-22			Gall-bladder draining	12	16	
	50		1-23-22				11	14	
26	51	P.	1-12-22	45	F.	Chronic polyarthritis	20		
	52		1-16-22				13		
	53		1-18-22				13		
27	54	A.	1-27-22	48	F.	Neurosis	14	30	
	55						13	23	
28	56	W.	2- 6-22	45	M.	Gout	13	26	

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
29	57	W.	12-24-21	25	M.	Addison's disease	20	22	
	58		12-27-21				12	14	
	59		1-11-22				10	16	
30	60	R.	1-18-22	26	F.	Pregnancy (8 mos.)	13	15	
31	61	W.	2-10-22	30	F.	Post eclampsia	13	16	
32	62	S.	1-12-22	40	F.	Cholecystitis	12		
	63						20		
	64						12		
	65						20?		
	66						21		
33	67	C.	5-9-22	30	M.	Epilepsy, polycythemia	12	14	
34	68	A.	3-9-22	25	M.	Bichloride poisoning	15	17	
35	69	B.	1-26-22	48	M.	Cancer stomach (inoperable)	15	18	
36	70	K.	3-24-22	40	M.	Normal	14	16	
	71		3-28-22				19	19	
37	72	L.	1-18-22	32	F.	Pregnancy (8 months)	14	18	
38	73	H.	3-19-22	42	F.	Cholelithiasis	15	25	
	74						14	25	
39	75	M.	4-3-22	24	F.	Subacute cholecystitis	15	16	
40	76	M.	3-3-22	50	..	Cholecystitis and cholelithiasis	15	18	
41	77	P.	2-18-22	50	F.	Eclampsia (3 days after delivery)	15	16	
42	78	T.	3-30-22	38	F.	Hyperacidity, cholecystitis	15	18	
43	79	T.	3-4-22	38	F.	Chronic cholecystitis	16	18	
44	80	M.	3-1-22	40	F.	Aortic aneurysm	18	35	Faint.
45	81	J.	1-20-22	55	M.	Chronic alcoholism	17	19	
	82		1-21-22				14	16	
	83		1-24-22				15	17	
46	84	C.	1-17-22	29	M.	Diabetes (severe)	16	19	
47	85	B.	4-6-22	65	F.	Cancer pancreas and liver (non-obstructive)	16	45	
48	86	F.	3-1-22	40	F.	Visceroptosis	18	20	
49	87	B.	1-17-22	22	M.	Syphilis (secondary)	17	19	
	88						19	22	
50	89	S.	1-17-22	18	M.	Rupture of liver	19	21	
51	90	A.	1-17-22	32	M.	Thyrototoxicosis	12	16	
	91		1-19-22				22		
52	92	S.	1-14-22	45	M.	Appendicitis	19	22	
53	93	B.	2-6-22	36	M.	Typhoid (convalescing)	21		
	94		2-8-22			Acute cholecystitis	14		
	95		2-20-22				15	30	
	96		2-23-22				20	20	
54	97	S.	12-23-21				20	22	
55	98	S.	12-24-21	58	M.	Malnutrition	20	22	
56	99	W.	3-23-22	70	M.	Chronic cholecystitis with cholelithiasis	10	22	Intermittent.
	100		3-17-22				14	25	
	101		3-21-22				15	16	Faint.
	102		3-27-22				12	16	
57	103	Y.	3-12-22	26	F.	Chronic cholecystitis, neurorosis	20	20	Faint.
58	104	C.	1-10-22	11	F.	Epilepsy, hyperpituitarism	21		
59	105	A.	1-5-22	65	M.	Pancreatitis, cholecystitis, cholelithiasis	21	25	
	106						20	26	
	107						22	27	
60	108	B.	2-16-22	70	M.	Chronic cholecystitis	22	22	Faint after 22 min.
61	109	H.	2-8-22	45	M.	Chronic cholecystitis	22	26	
62	110	H.	.....	62	M.	Chronic cholecystitis, cholelithiasis	23	33	
							23	33	
	111		3-25-22						
63	112	S.	2-10-22	55	M.	Diabetes (moderate)	25	25	Faint.
64	113	W.	2-24-22	3	M.	Hepatitis	0 in 1/2 hr.	(subcutaneously).	
65	114	C.	5-1-22	55	M.	Cirrhosis of liver (fatal)	0 in 120 min.		
	115						0 in 60 min.		
66	116	W.	3-21-22	45	F.	Chronic pancreatitis, hydrops of gall-bladder	0 in 120 min.		
	117		3-19-22				0 in 60 min.		

No. of cases.	No. of observations.	Name.	Date.	Age.	Sex.	Diagnosis.	Phthalein excretion.		
							Initial time.	Time of maximum intensity.	Character of flow.
67	118	W. S.	4-12-22	58	M.	Chronic pancreatitis	0 in 50 min.		
	119		2- 4-22				0 in 240 min.		
	120		2-20-22				0 in 75 min.		
	121		2-24-22				Faint in 120 min.		
	122		2-17-22				0 in 75 min.		
68	123	S.	12-23-22	25	F.	Eclampsia (1st test while in eclampsia, just after convulsion; last test after recovery)	45 45		
	124		2- 1-22				0 in 40 min.		
	125						0 in 180 min.		
69	126	T.	1-10-22	70	F.	Cancer head pancreas with obstruction	195 faint		
	127						18		
70	128	S.	1-11-22	50	F.	Cancer head pancreas, cholecystgastrostomy	0 in 2 hrs.		
	129						0 in 2 hrs.		
71	130	W.	2-13-22	3	M.	Cirrhosis of liver	0 in 120 min.		
	131		2-21-22				0 in 45 min.		
72	132	S.	3- 2-22	38	F.	Cholelithiasis, acute cholecystitis	20 very faint	90	until 45 min.
	133		2- 7-22				21	24	
73	134	G. L.	2-20-22	45	M.	Cancer stomach	18	22	
	135		2-22-22				24 faint	24	
	136		2-27-22				18		
	137		2-14-22				21	24	
	138		3- 2-22				18	20	
74	139	L.	1-11-22	74	F.	Stone in common duct	21	28	
	140		5-13-22				0 in 40 min.		
75	141	B.	5-15-22	45	F.	Starvation (4 to 8 days)	0 in 40 min.		
	142		5-16-22				19	35	
	143		5-17-22				17	20	Faint.
	144		2-25-22				19	29	Intermittent.
	145		3- 8-22						
76	146	B.	3-20-22	73	M.	Stone in common duct, cholangitis (severe)	40		
	147		3-21-22				14	47	
	148		1-21-22				19	19	Intermittent.
	149		1-22-22						Very faint.
77	150	B.	1-23-22	46	F.	Cholelithiasis, cholecystitis, syphilis of liver	35	78	
	151		2-13-22				60	60	Very faint.
78	152	G.	5-18-22	55	..	Stone in common duct	25 single	spurt at	25, none after.
	153		4- 6-22				70 faint,	intermitt	tent pale bile.
79	154	M.	4-20-22	44	F.	Stone in common duct	36	36	Faint, intermittent.
	155		3-13-22				40		
80	156	B.	4- 1-22	52	M.	Cirrhosis of liver, syphilis	45 faint	120 normal.	
	157						0 in 3 hrs.		
81	158	T.	4-13-22	30	M.	Cancer head pancreas (obstructive)	0 in 75 minutes		
	159		4-21-22				0 in 3 hrs.		
82	160	C.	6- 2-22	18	F.	Pregnancy, cholelithiasis	18	34	
	161		5-29-22				45 faint		
83	162	S.	5-26-22	35	M.	Intestinal toxemia			
	163		5-30-22				20	25	
84	164	R.	5-22-22	50	M.	Adrenalin M V (h)	16	28	
	165		5-23-22				15	20	
85	166	G.	5-20-22	26	F.	Dysentery	20	20	
	167		6- 5-22				13	35	
86	168	J.	6- 6-22	30	M.	Chronic cholecystitis	10	25	
	169		6- 6-22				10	55	
87	170	H.	6- 6-22	30	M.	Biliary stasis	0 in 3 hrs.		
	171		6- 6-22						
88	172	Dr. B.	6- 6-22	50	M.	Biliary stasis			
	173		6- 6-22						
89	174	Dr. B.	6- 6-22	50	M.	Atrophic cirrhosis			
	175		6- 6-22						

Sex. In 56 males, the average time of excretion was thirteen and seven-tenths minutes; and in 37 females, thirteen and nine-tenths minutes. There is therefore no difference attributable to sex. Aaron reports an average of seventeen and two-tenths minutes in 10 normal individuals, utilizing the same quantity of dye, while Piersol's results, using double the quantity in 15 normal individuals, were lower than ours by several minutes.

*Pregnancy.* Uncomplicated pregnancy in 8 instances showed an average excretion of fourteen minutes, viz., somewhat below the average normal.

*Diabetes.* There were 2 instances with an average excretion time of twenty-five minutes and sixteen minutes, averaging nineteen and a half minutes. There appeared to be no relation as to the severity of the disease to the rate of excretion of the dye.

*Epilepsy.* In 3 cases of epilepsy the readings were twenty-one minutes; twelve minutes and eleven minutes. The average was fourteen and nine-tenths minutes.

*Psychoneurosis.* The average excretion of 9 cases was twelve and eight-tenth minutes.

*Toxemias.* Three cases of eclampsia examined immediately after the convulsive stage, average fifteen minutes. A fourth case was done during the stage of convulsions and repeated 4 times as the patient improved. In this case the results were parallel with the condition of the patient. At first there was no excretion in forty minutes; when the patient had a convulsive seizure and removed the tube; at the second trial there was no excretion in one hundred and eighty minutes; in the third, there was just a trace one hundred and ninety-five minutes and in the last, when the patient's symptoms had cleared up, the time of excretion was normal, namely eighteen minutes. In a case of bichloride poisoning, three days after the patient had taken 12 gr. there was no delay in the initial appearance of the phthalein; the patient, however, had but the mildest symptoms at the time of the examination.

*Malnutrition.* The average appearance in 2 instances was fifteen minutes.

*Catarrhal Jaundice.* In 2 subsiding cases the average was ten and a half minutes.

*Endocrine Disturbances.* A case of Addison's disease averaged fourteen minutes for 3 tests; 1 of hyperpituitarism with epilepsy was twenty-four minutes; 1 of thyrotoxicosis averaged seventeen minutes.

*Syphilis.* In 2 cases of secondary syphilis, the average secretion was noted in sixteen minutes in 4 examinations. Several cases of syphilis with complications are summarized in the accompanying table.

*Acute Infections.* Five tests in 2 typhoid fever patients averaged fifteen and eight-tenths minutes.

*Cholecystitis with Cholelithiasis.* The rate of excretion in 40 cases of cholecystitis averaged seventeen minutes.

*Stone in the Common Duct with Jaundice.* The average rate of excretion was twenty-eight minutes in 9 cases. In 5 others there was no excretion whatever of the dye during the entire period of examination.

*Cancer of the Liver.* In a case which came to autopsy two days following the test, the time of excretion was twenty-five minutes; in another instance it was forty-five minutes.

*Atrophic Cirrhosis of the Liver.* In 2 instances of this affection, there was no excretion in two hours or in forty-five minutes respectively, when the tube was removed.

*Cancer of the Pancreas.* In 1 case there was no excretion in 3 tests in two hours; in the second, the average rate was forty-five minutes.

*Jaundice Following the Use of Arsphenamine.* In one instance there was no excretion in seventy-five minutes.

*Cardiac Disease.* In a single case of myocarditis the rate of excretion was eighteen minutes; in 1 of chronic passive congestion, two weeks before death, it was thirteen minutes.

**Conclusions.** From the examinations made by us, as well as those by Aaron and others, regarding the phenoltetrachlorphthalein test for liver function, we believe the following conclusions may safely be drawn.

1. The phenoltetrachlorphthalein test is a valuable means of determining liver function.

2. In order to obtain reliable results the technic in performing the test must be carefully carried out in every detail. On this account the preparation utilized must be stable and free from all deterioration.\* The tube must be *in situ* and the drip well established. Under these conditions, the end-result is definite and distinct and there is little or no difficulty in noting the maximum appearance of the dye.

3. In normal individuals the appearance of the excretion as measured day by day is extremely constant; the average being, according to our experience, in thirteen and seven-tenths minutes. A delay of more than twenty-three minutes in the excretion of the dye indicates the presence of some hepatic disease or mechanical obstruction at some point between the biliary ducts and the ampulla of Vater. The most marked delay occurred in biliary cirrhosis; in obstruction the delay varied from day to day when the obstruction was due to stone.

4. The test has proved useful as a means of checking up the technic of non-surgical biliary drainage. It is also of value in the diagnosis of cirrhosis and carcinoma of the liver and obstruction of the common duct from stone or tumor.

The manner in which the tetrachlorphthalein flows may aid in differentiating cases in which there is delay, especially between cholelithiasis, cancer and cirrhosis of the liver and external causes

\* The phenoltetrachlorphthalein ampules in stable form used in the performance of these tests were furnished us by Messrs. Hynson, Westcott and Dunning, of Baltimore, to whom we desire to acknowledge our thanks and from whom this preparation can now be obtained.

of obstruction. The flow in cases of calculus is usually intermittent and presents a greater variation from day to day, whereas in cirrhosis and other forms of obstruction, the flow after once beginning is constant and there is but an extremely slight daily variation.

5. Finally from these observations it is evident that the tetrachlorophthalein test is of considerable value as a means of determining liver function, and when properly performed may be of great aid in diagnosis.

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### PHYSIOLOGY OF THE EXTRAHEPATIC BILIARY SYSTEM AND ITS APPLICATION TO SURGICAL THERAPY.\*

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THE primitive gastro-intestinal tract is a simple tube occupying the midline position. Embryologically it is divided into three portions: the foregut, the midgut and the hindgut. The stomach, duodenum, liver, biliary ductal system and pancreas are derivatives of the foregut, and within this alimentary segment every digestive enzyme is elaborated and the mechanical and attritional processes of digestion carried out.

The stomach may be said to subserve two functions, namely, secretion and motion. Of these two, motor function is preëminently the most important. Digestion may be maintained for years with very little general disturbance of health so long as the motor function or evacuating power of the stomach remains intact. On the other hand, conditions associated with either loss of the normal evacuating power of the stomach or with a stenosis at the pylorus very quickly come to the physician for relief.

Contrary to the usually accepted idea of gastric physiology, the terminal portion of the stomach is alkaline and in the fasting or resting phase of the stomach there is a reflux of duodenal mate-

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rial into the antral portion, the acidulation and acid digestion of gastric contents taking place in the proximal two-thirds.

With the exception of the anal canal, the gastro-intestinal tract is devoid of pain-producing nerve elements. Everywhere throughout its entire length the movements of the gastro-intestinal canal are rhythmic and accompanied by specific and intrinsic chemical activity.

In attempting to interpret disturbed physiology in dysfunction of the external biliary apparatus, we must recognize that the liver and its ducts are but one part of the alimentary system and physiologically conform to the fundamental neuromuscular mechanism that applies to the entire alimentary system. The underlying basis of physiological action of the gut tube is embraced in the so-called law of the intestine, a name given to it by Bayliss and Starling, sometimes called the law of contrary innervation of Meltzer. In simple language this law means that local stimulation of any segment of the intestinal tube causes a contraction above and a relaxation below the stimulated part. There is always a contracting impulse at the cephalic end and an inhibitory impulse at the caudal end.

As a corollary to the rhythmicity of gastro-intestinal movement, it has been demonstrated that whenever there is an irritation of the gut tube the portion above the point of irritation early participates in an exaggeration of its normal function. Meltzer maintains that "The law of contrary innervation is manifested in all functions of the animal body and a disturbance of this law is a factor more or less important in the pathogenesis of many disorders and diseases of the animal body." In the upright position the fundus of the gall-bladder is at a lower level than its outlet. This morphological arrangement is true of all viscera that contain fluid and presupposes the ability of the organ to exercise contractile power and expel at least some portion of its contents. The gall-bladder, however, is incapable of completely emptying itself and although non-striated muscle fibers are contained in its wall they are without any definite arrangement into a muscle layer and are too sparsely distributed to make a complete evacuating organ. In spite of the paucity of muscle fibers the gall-bladder undergoes spontaneous rhythmic contractions from eight to ten times a minute. The lymphatic supply to the external biliary system is extremely rich and there is no anatomical partition or barrier between the intrahepatic and extrahepatic lymphatic distribution. The bile within the gall-bladder is materially different from the bile secreted from the liver or from the bile contained within the ducts. The former is concentrated, darker in color, has a higher specific gravity and is chemically changed by the addition of mucin and nucleo-albumins. Rous and McMaster recently demonstrated that the passage of bile through the cystic



duct concentrated the bile from two to four times while the gall-bladder is capable of concentrating the bile ten times in twenty-four hours.

The secretion of bile is continuous, yet it is delivered into the duodenum intermittently. In other words, we have a continuous secretion with periodic delivery. Correlated with this is the fact that the secretory pressure of the bile, as it descends from the liver through the common duct, is by and of itself insufficient to overcome the sphincter of Oddi; even the addition of the contractile pressure of the gall-bladder is insufficient to overcome the normal tonicity of the sphincter. There is required for relaxation an inhibitory impulse to allow the ejection of bile into the duodenum. During the fasting state the duodenum is free from bile and it has been demonstrated that the introduction of acid chyme, peptone, albuminose or the irritation of the duodenal mucosa by a thread or a duodenal tube is sufficient to inhibit the sphincter of Oddi and cause the delivery of bile.

From a neuromuscular point of view the muscle fibers of the gall-bladder and the sphincter of Oddi at the ampulla of Vater are antagonistic in their action, and the contraction of the former implies relaxation of the latter in a normal physiological biliary system.

A word of caution should be uttered here against applying *in toto* experimental data derived from research work on the biliary apparatus of normal animals. Clinical medicine and surgery is concerned with the gall-bladder and biliary apparatus when it is diseased and the seat of dysfunction and the results of research can be applicable to human pathology only when research workers will operate upon sick animals or surgeons operate upon normal humans.

When we survey the gastro-intestinal tract we are impressed with the fact that in the scheme of Nature there are normal points of stasis. For example, at the pylorus, at the ileocecal sphincter and at the rectosigmoidal juncture we have normal points of stasis. In the gall-bladder we have also a point of natural or physiological stasis and we might well question if it is not possible for a physiological state of stasis to become lengthened out into a condition with distinct pathogenesis. In other words, we may pass from a physiological stasis into a pathological stasis.

The bile on its way from the gall-bladder to the cystic duct does not reënter the hepatic duct, as the latter is closed by the mechanical pressure caused by the acute angle at which the cystic duct joins the common duct. The sigmoidal curve of the cystic duct and configuration of the neck and ampulla of the gall-bladder prevent overdistention and explain the mechanism of "white bile" or pressure acholia referred to by Erdmann and Heyd.

The fact that Nature planned an intermittent delivery of bile

into the duodenum must have a reason. In the fasting state the duodenum is free from bile. Therefore, it must be conceded that in the absence of gastric contents bile should not be present in the duodenum. This is a functional advantage to the individual and represents a protective mechanism in order to have the duodenum empty of bile when there is no physiological demand for it. Morphologically, the bile is delivered just at the partition between acid and alkaline digestion, at the point of transformation of chemical activity from an acid to an alkaline medium. The evacuation of gastric material in small amounts and at frequent intervals corresponding to the relaxation of the sphincter of Oddi clearly predicates that the bile will be delivered into the duodenum in response to the normal physiological demand.

The bile is not purely an excretion, for the bile salts are reabsorbed and undergo a more or less continuous circulation. One has only to recall the very marked improvement that takes place in patients who are losing bile through common duct drainage when they are fed their own bile. So impressed are we that in all cases of common duct drainage we feed the patients their own bile. Cokeman shows that soon after a biliary fistula has been established the salts in the bile fall to one-tenth of the normal since reabsorption cannot occur. This suggests that normally bile salts are excreted and reabsorbed ten times before being destroyed or eliminated.

Bile is, therefore, delivered into the duodenum as the summation of three factors: The hepatic secretory pressure, the expulsive force of the gall-bladder plus the action of respiration with the ascent and descent of the diaphragm providing a milking action. The maximum pressure exerted by the three is insufficient to overcome the tonicity of the sphincter of Oddi unless another factor is brought into play, namely, the relaxation of the sphincter. It would seem that as the gall-bladder is incapable of completely emptying itself (in an examination of several hundred cadavers we have never seen an empty gall-bladder) it may be supposed that as the gall-bladder becomes distended it becomes supersensitive to further distention and initiates a neuromuscular reflex which induces the reciprocal half of the reaction, namely, the relaxation of the sphincter of Oddi. When the gall-bladder is absent naturally or after cholecystectomy the one-half of this relationship is lost and the stimuli for the alternate contraction and relaxation of the sphincter is absent. Accordingly, the sphincter ceases to function in the mechanism of biliary delivery so that in the cholecystectomized animal the biliary delivery is continuous and the change from intermittent delivery to a continuous delivery has been obtained by the extirpation of the gall-bladder.

Repeated dissections in animals without a gall-bladder show that the muscle fibers of the sphincter of Oddi are at all times

present but not active and in humans with an incomplete or partial cholecystectomy there is formed an artificial gall-bladder or the cystic duct dilates into an adventitious gall-bladder or diverticuli are formed throughout the ducts. In such cases we find that the sphincter regains its function and the intermittency of biliary delivery is again called forth.

At one time gall stones were considered the only pathological evidence of a diseased gall-bladder, and the finding of stones was interpreted as the essential pathological lesion. We now know that this is incorrect and that it is the infective process in the gall-bladder or the biliary system that induces the pathological changes and provides the surgical indication. It is the deeper tissues of the gall-bladder that are more particularly involved and 25 per cent of the lesions of the gall-bladder that require surgical intervention are characterized by the absence of gall stones. An infected gall-bladder, with or without stones, is an expression of a pathological change more widespread and extensive than that which is represented in the gall-bladder itself. It is possible to culture anaërobic bacteria from the bile radicals of the liver almost at any time and occasionally aërobes. Again, under normal conditions of health there are occasional bacteria in the blood stream and it is by no means a rare occurrence to have apparently normal bile contain pathogenic organisms in the process of being eliminated by the liver. In the liver we have an intermediate barrier between the systemic and portal circulation and it is reasonable to suppose that there are very few cases of cholecystitis which are without liver involvement. These changes, when of mild degree, are in the form of a hepatitis; Graham has demonstrated a microscopical picture of hepatitis in every operated case of cholecystitis.

There are four theoretical ways in which the gall-bladder could be infected. Of these, one presupposes a mucosal infection, the infecting organism reaching the gall-bladder either by ascent from the duodenum or descent from the liver. Laboratory experiments demonstrate that it is with the utmost difficulty that the gall-bladder can be infected from within its cavity. The injection of virulent streptococci into the interior of the gall-bladder does not produce gall stones. Other pathological factors must be brought into play which lessen the resistance of the tissues beneath the mucosa. Coffey has demonstrated that the duodenum will rupture under pressure before there is a reflux of material up the common duct. It does not seem probable that cholecystitis commonly arises from infection by way of the mucosa. Two other possibilities for infection of the gall-bladder are the bringing of infectious material through the blood stream or by contact from contiguous viscera. If the blood stream is the means of infection we must distinguish a straight hematogenous infection

and an infection by means of the portal system. If the vascular systems were at fault one would expect that the liver tissue itself would show uniform changes throughout its substance, but this is not true, as we find that in infections of the gall-bladder it is the right lobe of the liver that is coincidentally involved and particularly that portion in intimate contact with the gall-bladder.

The fourth method for infecting the gall-bladder would be by means of the lymphatic circulation, and it has been proved by Sudler and the work of Franke, Sweet, Deaver and Pfeiffer that there is a very intimate and extensive lymphatic connection between the gall-bladder, liver, common duct and pancreas. Anatomically there is no separation between the extra- and intra-hepatic system of lymphatics and a hepato-lymphatic infection would offer a reasonable basis to account for most of the cases of cholecystitis. Rosenow, in a series of very beautiful experiments, demonstrated the possible source of cholecystitis from infectious emboli in the walls of the gall-bladder and drew attention to the relative affinity of certain types of bacteria for the tissues of the biliary apparatus. That this is a method of infection in certain cases cannot be denied, but it must be relatively infrequent by reason of the comparative rarity of embolic processes of the gall-bladder in any of the accepted forms of bacteriemia.

It seems logical to believe that in the majority of cases cholecystitis represents a direct infection of the wall of the gall-bladder from an infected liver. Infection reaches the liver by the portal vein, involves the periportal tissues and induces a pericholangitis with involvement of the intra- and extrahepatic lymphatics, thereby bringing by direct extension an infection of the walls of the gall-bladder. This would offer an explanation for the cholecystitis that is coincident with appendicitis, peptic ulcer, typhoid fever and suppurative hemorrhoids.

It has been our experience that the diseased gall-bladders without stones are distinctly a greater menace to complete recovery and future well-being than is the less grossly changed gall-bladder with stones. The palpatory diagnosis of disease of the gall-bladder in cases not characterized by the presence of stones is fallacious, and an opinion as to the normality of a gall-bladder simply upon palpation through a lower abdominal wound is seriously open to question. There are, however, certain criteria which in the absence of calculi may collectively be taken to indicate that a particular gall-bladder is pathological. *Seriatim*, these may be defined as follows: (1) A loss of the normal color (under normal conditions the gall-bladder is never white, brown or mottled, but always possesses its distinctly olivary-green tinge); it is essential that the color of the gall-bladder be noted upon opening the abdomen, for upon exposure to the air it takes on a rather whitish appearance. (2) The walls of the normal gall-bladder are quite thin, and any marked increase in the mural thickness bespeaks

infection. (3) The deposition of saffron-colored fat well up to and on the fundus of the gall-bladder is distinctly abnormal and represents infiltration of the wall. (4) The presence of varying degrees of pericholecystitis is suggestive only; personally, we are unable to account for some of the many adhesions that exist between the duodenum and gall-bladder, including the so-called cystico-duodenal and cystico-colonic ligaments which Todd states are present in 1 out of 4 individuals; we have found adhesions so frequently in apparently normal persons without any disabling angulations and, so far as we can determine, in patients free from upper abdominal symptoms that the evidence of occasional adhesions between the gall-bladder and colon in the absence of symptoms must be accepted as of minor value in determining the degree of pathology in the gall-bladder. (5) The inability to express bile from the gall-bladder by manual compression is of very little diagnostic importance and is not necessarily indicative of pathological change; by the peculiar "S"-shaped conformation of the cystic duct and ampulla the gall-bladder can be distended almost to the point of rupture without allowing any bile flow through the cystic duct; adhesions angulating the cystic duct can bring about the same condition without intrinsic disease of the gall-bladder being evident. (6) The presence of hyperplastic lymph glands along the course of the cystic and common ducts is indubitable evidence of infection, past or present, of the biliary system for the mechanism of lymphadenitis is the same in the biliary system as it is elsewhere in the body and adenitic hyperplasia represents infective irritability. (7) The finding of a papillomatous mucous membrane rather than the normal smooth type, with minute cholesterol crystals imbedded in its substance, is of primary importance in the diagnosis of the so-called strawberry gall-bladder; we place little value in the so-called inspissated bile as an evidence of infection primarily, because it is the normal condition for bile to be inspissated or concentrated within the gall-bladder. (8) The presence of white plaques extending from the serosal covering of the gall-bladder to the under surface of the liver; they represent, to our mind, fibrosis in liver tissue concomitant or sequential to gall-bladder infection.

**Conclusion.** We may say that with a normal liver and biliary system the plan of biliary secretion and elimination is excellent. Surgery, however, is undertaken for diseased conditions of the biliary system and increasing clinical experience demonstrates that ablation of the gall-bladder is without any change in the health or metabolic processes of the individual. By reason of the fact that infection in the gall-bladder is preponderantly a mural pathology, the most reasonable and best means of curing this condition and interrupting the vicious circle of liver-gall-bladder infection and gall-bladder-pancreas infection is to remove the gall-bladder, namely, cholecystectomy.

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# QUANTITATIVE DETERMINATION OF ENZYME ACTIVITY IN DUODENAL FLUIDS.\*

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OF the many methods which have been proposed for the determination of the pancreatic enzymes, those of Gaultier<sup>1</sup> have appeared to us to possess advantages of simplicity and availability for such estimations in duodenal contents. We are here presenting certain modifications of the technic of these methods which we believe increase their accuracy and usefulness in the analysis of small quantities of such duodenal contents.

The enzymes determined are trypsin, amylase, and lipase. For trypsin gelatin is used as a substrate and the amino groups liberated during digestion estimated by alkali titrations after formaldehyde addition. We have reduced the quantities and strength of the gelatin solution employed in this test, thus making it more available for the determination of low tryptic activities.

Amylase is determined by estimating the maltose formed from a given amount of soluble starch. Merck's soluble starch (Lintner) was used instead of potato starch because of much greater ease of manipulation and preservation. Results are not calculated to starch as suggested by Gaultier, but expressed as maltose. The maltose is determined by Benedict's method instead of by the procedure of Grimberty.

Lipase is determined by its action upon an emulsion of olive oil,<sup>2</sup> the acidity developed being titrated. Gaultier used lecithin in his experiments. On account of the difficulty and cost of obtaining lecithin and the wide variations in composition of lecithin preparations obtainable, we have used an olive oil emulsion, made as suggested by Palmer<sup>2</sup> and titrated in alcohol-ether solution instead of in absolute alcohol.

The methods are relatively rapid, digestion periods of only one hour being required. Determinations should be made as soon as possible after obtaining samples which should be kept in the ice box until used. The methods in detail follow.

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<sup>1</sup> Gaultier, Roche and Baratte: *Paris Médicale*, 1919, 32, 115.

<sup>2</sup> Palmer, L. S.: *Science*, 1920, 4, 2.



**Procedure.** (a) Prepare three 50 cc Erlenmeyer flasks, marked "T," "A," and "L" (trypsin, amylase, and lipase).

(b) To flask "T" add 20 cc of 5 per cent solution of gelatin.<sup>3</sup> To flask "A" add 20 cc of 5 per cent solution of soluble starch.<sup>4</sup> To flask "L" add 5 cc of 20 per cent emulsion of olive oil.<sup>5</sup>

(c) To each flask add one drop of phenolphthalein solution (1 per cent alcoholic solution); add to each flask, by means of an Ostwald pipette, 1 cc of duodenal fluid.

(d) To each flask add, drop by drop, from a burette,  $\frac{N}{10}$  NaOH until a light pink color is produced which persists on shaking.

(e) To flask "A" add, drop by drop, from a burette,  $\frac{N}{10}$  H<sub>2</sub>SO<sub>4</sub> until the first disappearance of pink color; incubate flasks for one hour at 37° C., shaking the flasks every fifteen minutes.

(f) Upon removal from incubator place "T" and "L" flasks in ice water and add to the "A" flask a small amount of sodium carbonate, to stop digestion.

(g) Controls of boiled duodenal fluid, plus gelatin, starch and oil, treated as above stated, must be incubated with the three test flasks and correction for these blanks made.

(h) *Tryptic Activity.* (Formol Titration.) Add 5 cc of neutral formol-alcohol solution.<sup>6</sup> Titrate again to the first light pink color with  $\frac{N}{10}$  NaOH. From the burette reading subtract the blank reading. The result is a measure of the peptones, amino-acids, etc., formed by the action of the trypsin of 1 cc of the duodenal fluid upon 1 gram of gelatin.

(i) *Lipolytic Activity.* Add 10 cc of neutral alcohol-ether solution.<sup>7</sup> Titrate to neutrality with  $\frac{N}{10}$  NaOH (first light pink color). Take the burette reading. Subtract the blank reading.

<sup>3</sup> Gelatin solution (5 per cent). Dissolve 50 grams of highest grade culture media gelatin in a liter of distilled water in a large beaker over a Bunsen burner. The temperature of the water should be kept below 60° C., to prevent scorching of gelatin. Stir continuously until gelatin solution is homogeneous. Pour carefully into a clean, previously heated bottle (to prevent cracking) and add toluene to cover gelatin solution with  $\frac{1}{4}$  inch layer. Keep in a warm place.

<sup>4</sup> Soluble starch solution (5 per cent). Stir 50 grams of soluble starch up into a smooth paste in a mortar after adding slowly 50 cc of cold distilled water. Heat to boiling 950 cc of distilled water and add to this, with continuous stirring of the starch until a homogeneous mixture results. Pour carefully into a clean, previously heated bottle and add toluene to cover the starch solution with  $\frac{1}{4}$  inch layer. Keep at room temperature.

<sup>5</sup> Olive oil emulsion (20 per cent). There are required 30 grams of gum acacia, 60 cc of distilled water, and 120 cc of best quality olive oil. Place the acacia in a mortar, add the oil, rub into smooth paste, always stirring in one direction. When a thick, homogeneous paste results, add, all at once, the 60 cc of water and continue stirring until a milk-white emulsion is formed. Measure into a graduated cylinder and add distilled water with repeated washing of mortar until 600 cc of emulsion is made. Add 1 cc of 40 per cent formalin as preservative. Keep in ice chest.

<sup>6</sup> Formol-alcohol solution. Mix equal parts of 95 per cent alcohol and 40 per cent aldehyde solution. Make neutral to phenolphthalein with concentrated NaOH, added drop by drop, to faintest pink color.

<sup>7</sup> Alcohol-ether solution. Five parts of neutral 95 per cent alcohol and 1 part of acid-free ether are mixed fresh for each day's determinations. Of this mixture, made neutral with N/10 NaOH, 10 cc are used in each test.

The result is a measure of the fatty acids formed by the action of 1 cc of duodenal fluid upon 1 cc of olive oil for one hour at 37° C.

Lipase appears to require, for its proper action, the presence of some constituent of the bile. Where, therefore, as in certain liver and gall-bladder disturbances, there is a restricted flow of bile into the intestine, 1 cc of fresh ox bile or a small amount of the mixed bile salts in powder form (Fairchild and Foster's bile salts were found satisfactory) should be added to the digestion mixtures in carrying out the lipase determination.

(j) *Amylolytic Activity.* Pour the digestion mixture into a 10 cc burette and run slowly, then drop by drop, into 5 cc of Benedict's reagent,<sup>8</sup> plus one to two gms. of sodium carbonate, heated to boiling in a large test tube until the last trace of blue color disappears. The burette reading, divided into 0.0149 (the number of grams of maltose required to reduce 5 cc of Benedict's reagent) gives the amount of maltose in 1 cc of the digestion mixture. Multiply by 20 to obtain the total amount of maltose formed.

The following technic was employed for obtaining duodenal specimens.

The patient is examined in the morning on an empty stomach. It is best to measure the distance from the incisor teeth to the umbilicus in each individual, marking the tube with a piece of thread. The tube is then passed with the aid of a little water to this mark. The patient is given one or two glasses of water slowly while the tube is introduced to the second mark, usually corresponding to the duodenum. This passage requires usually ten or fifteen minutes, and the patient is turned to his right side with the pelvis tilted in such a position that the left leg is drawn up over the right leg. This insures sufficient rotation to facilitate peristaltic action of the stomach. The tube in many instances has reached the duodenum in one-half to three-quarters of an hour. In other cases, two hours or more are necessary, depending on the type of stomach, the intensity of the peristaltic waves, and also the question of pylorospasm or a lesion of the pylorus. In some instances it is impossible to perform duodenal intubation under less than several hours, but in the average case the tube is readily passed

<sup>8</sup> Benedict's sugar reagent.

Copper sulphate (crystallized)	18.0 grams
Sodium carbonate (crystallized) (one-half the weight of the anhydrous salt may be used)	200.0 "
Sodium or potassium citrate	200.0 "
Potassium thiocyanate	125.0 "
Potassium ferrocyanide (5 per cent solution)	5.0 cc
Distilled water to make a total volume of	1000.0 "

With the aid of heat dissolve the carbonate, citrate, and thiocyanate in enough water to make about 800 cc of the mixture and filter if necessary. Dissolve the copper sulphate separately in about 100 cc of water and pour slowly into the other liquid with constant stirring. Add the ferrocyanide solution, cool, and dilute to exactly 1 liter. The copper salt only need be weighed with exactness.

into the duodenum within one half to two hours. After the patient has maintained the right-sided position, if he show no bile, we make it a point to encourage him to walk around and then again assume the right-sided position, a procedure which not infrequently brings about satisfactory results. When the tube is in place, allow the patient to drink a cup of hot water in which two bouillon cubes have been dissolved. When the characteristic syrupy bile is obtained, the tube is maintained in one position and specimens are withdrawn.

In the following table are given a series of results obtained on duodenal fluids using these methods. They are not to be considered as characteristic of the particular disorders mentioned, as further study, and especially a more standardized technic in the collection of specimens, is required before definite values can be assigned. The methods of enzyme determination, however, we believe will prove of value in further studies of this kind. We considered the use of buffer substances as additions to our digestion mixtures to regulate the reaction of these,<sup>9</sup> but found that consistent results were obtained without such additions, which have the disadvantage of interfering with the alkali titrations. In each case our mixtures are brought to a definite reaction at the start by titration, so that results obtained with duodenal contents of varying reaction should still be comparable.

#### THE ENZYME CONTENT OF DUODENAL FLUIDS.

No.	Diagnosis.	Trypsin, cc N/10 acid.	Amylase, maltose formed (grams).	Lipase, cc N/10 NaO
1	Cholecystitis . . . . .	3.5	0.10	0.78
2	Diabetes mellitus . . . . .	2.6	0.17	0.00
3	Cholecystitis . . . . .	6.0	0.25	1.00
4	Myocarditis . . . . .	8.3	0.30	4.50
5	Diabetes mellitus . . . . .	9.0	0.33	4.15
6	Intestinal stasis . . . . .	3.2	0.17	1.35
7	Cholecystitis . . . . .	0.4	0.25	0.25
8	Duodenitis. Cecal adhesions	2.7	0.13	2.80
9	Duodenitis. Cecal adhesions	1.25	0.18	3.20
10	Cholecystitis . . . . .	5.60	0.34	2.35
11	Cholecystitis . . . . .	2.65	0.42	10.70
12	Cholecystitis . . . . .	2.20	0.42	7.50
13	Cholecystitis . . . . .	3.60	0.24	6.70
14	Cholecystitis . . . . .	4.50	0.42	7.65

**Conclusions.** Methods are described for the determination of trypsin, amylase, and lipase in duodenal contents. These methods have the advantage of simplicity and are believed to be sufficiently accurate for clinical work.

\* McClure, Wetmore and Reynolds: Arch. Int. Med., 1921, 23, 706.

## ANTIPNEUMOCOCCUS SERUM IN LOBAR PNEUMONIA. A CLINICAL REPORT.\*

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IN the spring of 1917, the serum treatment of lobar pneumonia was begun on the medical wards of Gouverneur Hospital. The technic of administration of the serum was learned first hand from Dr. Rufus Cole and his co-workers at the Rockefeller Hospital, Monograph No. 7, from the Rockefeller Institute not being published until October 16, 1917. The technic, as given in that publication, we have followed with such modifications as will be given below.

Antipneumococcus serum was supplied us by the Rockefeller Hospital, there being none on the market at that time. Dr. Park, of the New York Board of Health, differentiated the sputum for us, as we did not, at that time, have any one in our laboratory familiar with the technic.

From the spring of 1917 to the present all cases of lobar pneumonia, *clinically*, have been systematically treated with antipneumococcus serum excepting at such times as serum was not obtainable, and except from April, 1917, to October, 1919, during which time the writer was in military service, where, however, the treatment was continued and the results published.<sup>1</sup> The report of cases, observed in military service, comprising 139 lobar involvements, of varying bacteriology, is incorporated into the present report, which therefore represents continuous observation from April, 1917, to October, 1922.

The opportunity for clinical and laboratory observation in a municipal and military hospital differs, but this difference enabled one to study the treatment under such varied conditions that it proved to be a decided advantage in drawing conclusions as to its efficiency. For this reason the two reports are now combined.

Gouverneur Hospital is a municipal institution, situated in a thickly settled section of New York City. Though the hospital is small, the service is very active. The pathological laboratory, which is a subdepartment of the Bellevue Pathological Department, has a part-time pathologist, but it is not possible, even with the aid of the main laboratory at Bellevue, to do more than the routine work of the hospital. Moreover, the ambulance service is heavy and this together with the ward work occupies the interne staff constantly, so that research work is not possible, were it advisable.

\* Read by title at meeting of the Association of Am. Phys., Washington, D. C., May 2, 3 and 4, 1922.

<sup>1</sup> AM. JOUR. MED. SCI., 1918, 156, 887.

A treatment to be of general value must be applicable in just such a field of work as our hospital affords. A patient with an easily recognizable, but rapidly progressing pathological condition (lobar pneumonia) is admitted to such a hospital and immediate treatment is indicated. A thoroughly equipped research institution (the Rockefeller Institute and Hospital) presents, through its publications, an efficacious and (if properly administered) harmless treatment. The question is, can this treatment be applied in the *field work* of medical practice? This report is then a record of field work on cases *clinically* presenting signs and symptoms of lobar pneumonia and treated with antipneumococcus serum.

For the reasons given above, sputum differentiation could not be carried out in all cases. When possible the sputum was differentiated, frequently subsequent to the administration of the serum, for we consider that this examination does not justify delaying the treatment. We have regarded the prompt administration of antipneumococcus serum in the same way as one regards the prompt administration of antimeningococcus serum in cases showing meningeal involvement.

The clinical diagnosis of lobar pneumonia offers little difficulty, as a rule. The bacteriological diagnosis, in the absence of routine sputum differentiation, cannot, of course, be made; but out of 529 cases of lobar pneumonia, reported in the Rockefeller Monograph No. 7, 454 were due to the pneumococcus, and out of 139 cases in the military service (report referred to above) 81 cases were due to the pneumococcus. It is therefore reasonable to expect that, in a series in which routine sputum differentiation was not done, a correspondingly large percentage of pneumococcus infection would occur. Autopsies could not be obtained in all fatal cases, but except for the bacteriology, there is little to be added by an autopsy on this condition, that cannot be determined at the bedside.

In the spring of 1917, Type I serum only was used, and following the instructions contained in the Rockefeller Monograph all other types were untreated with serum. At first we waited for the report on the sputum before giving the serum. This often caused a delay of many hours, owing to the difficulties mentioned above. The sputum was often not satisfactory for the bacteriological examination, making the report indefinite. This determined us later to administer the serum without waiting for the sputum report, the result being that many hours of valuable time were gained for the patient. In the military service series from 1917 to 1918, in addition to this immediate administration, on making the clinical diagnosis, we used polyvalent serum in all cases of lobar consolidation, with 2 deaths in 81 cases of pneumococcus infection (see report referred to above). This low mortality, together with the marked freedom from the clinical toxic mani-

festations, so common in this disease, led us to adopt the polyvalent serum in Gouverneur Hospital on resuming active service in that institution in 1920. That polyvalent serum is efficacious in the other types we are convinced from clinical observation, though we recognize that this has not been proved by laboratory investigation. This will be further discussed under "serum" below.

In the absence of routine sputum differentiation, we have been compelled to include all cases of lobar consolidation, of whatever bacteriology. Knowing the greater virulence of streptococcus infection alone, or complicating pneumococcus, this inclusion of all cases of whatever bacteriology, would tend to increase the mortality figure considerably. This must be borne in mind in considering the figures given below. On the other hand we feel that the circumstances in which we had to administer the treatment were such as prevail in many hospitals throughout the country, and were not such as are to be found in a few institutions with full laboratory personnel and equipment. The question as to whether the treatment is applicable to general use or whether it can be used for those cases only, for whom all facilities are available, is we think answered by our experience at Gouverneur Hospital.

The question of expense is a serious one, yet when one considers the high position of pneumonia in mortality statistics and the fact that, if the patient is enabled to combat the disease at the most virulent stage, his recovery in the large majority of cases is complete, and that he is fully restored to health and activity, this expenditure seems justifiable, especially in a community of wage earners. The authorities of our Hospital have taken this attitude regarding the purchase of serum.

In Table I are given the mortality figures of the different forms of pneumonia considered. As will be seen, the epidemic, at which time serum was not being used, was very virulent, making the mortality unusually high, as was experienced everywhere. To include these figures would increase the *non-serum mortality* in a misleading way, so for this reason they are omitted.

TABLE I.—MORTALITY OF ALL TYPES OF LOBAR PNEUMONIA  
(MUNICIPAL AND MILITARY) NON-EPIDEMIC.

	Non-epidemic, 603 cases, received serum.	Treated without serum.	Epidemic, 105 cases, all treated without serum.
Recovered . . . .	210	252	35
Died . . . . .	34	107	70
Total . . . . .	244	359	105
Mortality . . . .	13.9%	29.8%	66.7%

Had serum been used on any of these cases the figures would be included, but the epidemic occurred during the years that

serum was not being employed. Toward the end of the epidemic the writer returned to duty at the Hospital, but it was some time before the serum could be procured. The cases are mentioned because they occurred in the current years which we are considering.

If we take the municipal cases separately we find they show a mortality much higher than the military, which is to be expected (Table II).

TABLE II.—MORTALITY OF DIFFERENT KINDS OF LOBAR PNEUMONIA.

	Municipal cases.	Military cases. (All types bacteriologically).	Military cases. (Pneumococcus only.)
Recovered . . . .	82	128	79
Died . . . . .	23	11	2
	<hr/>	<hr/>	<hr/>
Total . . . . .	105	139	81
Mortality . . . .	21.8%	7.8%	2.4%

In whatever way these figures are considered, whether separately or together, the mortality of the serum cases is distinctly below that of the non-serum cases.

**Analysis of Cases.** The changing personnel of a hospital staff makes it difficult to obtain uniform notes and this is especially experienced when the observations extend over several years. Recognizing this difficulty we have limited our analysis of cases to those data which are subject to the least error, thus:

*Day of disease, diagnosis, age, serum* whether given or not; amount at each dose; total amount given: *Result*, recovered or died.

For our own study we have considered *the sputum type; the complications; the number of days patient was in the hospital; the autopsy findings; the extent and location of the consolidation*. But these latter are not analyzed in this report for reasons given above.

*Day of Disease.* This is perhaps the least reliable of the data which we selected to analyze. Many of our hospital cases, of whatever disease, remain at home or at work several days after they should have had medical care. Pneumonia, however, rapidly assumes serious features and is less likely than other diseases to permit the patient to put off seeking medical aid. Pain in the side, cough, fever, giving up work and going to bed have been the features which we considered marked the onset of the disease. Unreliable as this information sometimes is, we have enough trustworthy answers to state that the prognosis becomes increasingly less favorable when serum is begun *after the third day of the disease*. Serum administered in the first twenty-four to thirty-six hours offers the best prognosis, as will be seen by the low mortality in the military service, in which all cases were referred for treatment not later than the second day.

*Age.* Children are not included in this analysis, the pediatric service in this hospital being separate from the adult medical service. The cases ranged between the ages of fourteen and seventy-five years. The ages will be further considered under "mortality."

*Diagnosis.* This of course allows of error, but many cases can be diagnosed in the first thirty-six hours, and few are doubtful after the second day.

*Serum.* We have used polyvalent serum. Experience in the military service was clinically convincing that polyvalent serum was an active agent in other than Type I pneumonia. This we recognize is not proven bacteriologically. The research laboratory worker is compelled to limit his statements to what is demonstrable by laboratory tests. The clinician, at the bedside, *lacking these laboratory proofs*, makes observations with regard to duration of the disease, well-being of the patient, that is, degree of toxic manifestations, limitation of the pathological process, recovery, mortality, etc., all of which, if studied in a sufficiently large number of cases and within strict limitations, constitute *clinical evidence* which may precede and lead to subsequent laboratory proof. One would not withhold quinine in malaria or thyroid extract in cretinism or myxedema because the therapeutic mechanism of these agents is imperfectly understood. The cases here reported have been studied under such circumstances and are made public in the hope that other clinicians may add similar studies until the reports of many thousands of cases have been brought together. Until this can be done it is impossible to state conclusively whether we have in polyvalent serum an agent which will uniformly lessen the mortality of this destructive disease. It has been suggested that strains of pneumococci of varying degrees of virulence appear from time to time accounting for the variations in mortality. This is no argument against the use of an agent which will reduce the mortality of the infection which annually is present.

*Technic and Amount.* Desensitizing has been done by the subcutaneous method, using 2 cc, 3 cc and 5 cc at one or two-hour intervals. We have not thought well of the intradermal method, as its interpretation is too delicate and less suited to the varying personnel of an interne staff of a general hospital. 100 cc has been the usual dose and we have rarely had to give more than three such doses at twelve to twenty-four-hour intervals. The temperature of the serum and the slow administration into the vein have been carefully watched. No interne is permitted to give the serum without having had personal instruction and supervision by a senior house officer.

*Anaphylaxis.* One case of anaphylactic shock occurred in the military service, and 1 at present in the hospital at Gouverneur. Neither of these cases showed any sensitiveness by the ordinary desensitizing test. The military case showed signs of shock when



80 cc had been administered and the Gouverneur case when 30 cc had been given. In the Gouverneur case the serum had been given with the onset of the disease without any sign of anaphylaxis, and following the third dose the temperature subsided, but after a few days of lowered temperature new chest signs appeared and the temperature again rose. During the interval hypersensitiveness had developed, which however, was *not manifested by the subcutaneous desensitizing test*, and did not appear till 30 cc had been given.

Both these cases had a prompt fall in temperature, but both had a marked serum skin reaction. In such cases, adrenalin should be at once given and serum should be *immediately discontinued*. In the military case there was a history of asthma. It is important to refer to this small group of cases which fail to give signs of hypersensitiveness with the skin test. The desensitizing should never be considered as a mere routine to be relegated to untrained assistants and should be carried out with as close observations as the giving of the serum itself. About 50 per cent of the cases showed the ordinary signs of serum sickness, which lasted from two to ten days.

*Mortality.* The figures have already been given (Tables I and II). In Tables III and IV is given the mortality with regard to the *Day of the Disease* and the *Age of the Patient*.

TABLE III.—MORTALITY ACCORDING TO DAY OF DISEASE ON ADMISSION.

Day of admission.	Hospital.	No. of deaths.
7th or 8th . . . . .	Gouverneur	6
5th or 6th . . . . .	"	4
3d or 4th . . . . .	"	9
1st or 2d . . . . .	"	3
1st or 2d . . . . .	Military	11
Undetermined . . . . .	Gouverneur	1
Total . . . . .		34

TABLE IV.—MORTALITY ACCORDING TO AGE.

Age.	Hospital, number of deaths.	
75 . . . . .	Gouverneur	1
65 . . . . .	"	1
50 to 60 . . . . .	"	6
40 to 50 . . . . .	"	5
30 to 40 . . . . .	"	6
20 to 30 . . . . .	"	4
18 to 25 . . . . .	Military	11
Total . . . . .		34

I desire to express my thanks to Dr. Rufus Cole for looking over this report in the manuscript and to Drs. McNaughton, Fisher and Bogart, internes at Gouverneur Hospital for their assistance in going over the records,

## JUVENILE PARESIS: WITH A PRESENTATION OF TWENTY-THREE CASES.

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ALTHOUGH the possible relation of syphilis and general paresis was expressed by Esmarck and Jessen in 1857,<sup>1</sup> paresis in congenital syphilitics remained unrecognized until Clouston,<sup>2</sup> in 1877, described a case in a boy, aged sixteen years. Clouston pointed out that clinically and pathologically the disease that affected his patient in no way essentially differed from the adult form of the disease. This is true insofar as paresis is seen in adolescence, but, at an earlier period the symptomatology is distinctive and in many ways unlike that of adults.

There are few statistics concerning the incidence of juvenile paresis. According to the admission rate for all forms of psychoses into the institutions in this country during 1910, of 60,769 patients, 327 were under fifteen years of age and 17 of this number were paretics (11 males and 6 females). Between the ages of fifteen and nineteen, there were 2,539 patients admitted and 47 of these had paresis (28 males and 19 females). It is generally stated that juvenile paresis is rare. On the other hand, Kraepelin<sup>3</sup> states that it is not uncommon in his experience, since he can often demonstrate as many as 4 cases at one time in his clinic. According to Leonard,<sup>4</sup> there are about 250 cases on record (1915). Schmidt, Kraepelin and Toni<sup>5</sup> have recently reported a series of 54 cases which is the largest series reported.

The clinical picture of juvenile paresis is so unlike that of the adult form it was doubtless frequently overlooked in earlier times. Many juvenile paretics pass as cases of epilepsy or idiocy with epilepsy. Since modern diagnostic methods have been applied to the spinal fluid, a great aid has been given to the diagnosis of obscure cases. In the light of present knowledge the status of an epileptic or feeble-minded congenital syphilitic cannot always be defined accurately in the absence of a spinal fluid examination.

**Predisposing Causes.** The recent work of Levaditi and Marie<sup>6</sup> points strongly to the existence of a neurotropic strain of *Treponema pallidum* as the cause of paresis. When one visualizes neurosyphilis both in acquired and congenital syphilitics it becomes difficult to correlate experimental evidence of the existence of a neurotropic strain of *treponema* with clinical observation. In

addition to a possible neurotropic strain as a cause of paresis there are in all probability other and perhaps equally important determining factors. Alcoholism in the parents, psychopathic inheritance and cranial injuries have been given as predisposing causes. It is of interest to note that the majority if not all the causes which may be assigned in adults are essentially absent in the development of juvenile paresis. The determining factor in the localization of treponemata in the brains of juvenile and adult syphilitics with the production of pathological lesions characteristic of paresis is as yet unknown.

**PARESIS IN THE SECOND GENERATION. THE PROGENY OF PARETICS.** In many juvenile paretics, syphilitic infection can be demonstrated in the parents and frequently in the brothers and sisters. In Alzheimer's<sup>7</sup> 41 cases, syphilitic infection was demonstrated in 70 per cent of cases; in 17 out of 20 cases reported by Hirschl,<sup>8</sup> and in 80 per cent of Mott's cases. Indeed, cases have been observed in which one or both parents were paretics. Amelien reports 6 cases of juvenile paresis, the parents of whom were paretics. He observed these cases among 238 cases of paresis; in 1 case two brothers had paresis and a sister tabes. Rieger reports a family in which the father, son, daughter, and granddaughter had paresis. In Frölich's<sup>9</sup> cases, paresis existed in the parents in 16.4 per cent; in an additional 13 per cent there was either tabes, hemiplegia, or apoplexy in the parents.

The studies of Ricard<sup>10</sup> and those of Semper<sup>11</sup> show that a large percentage of the surviving children of paretics present signs of mental and physical inferiority. In Kraepelin's studies of 124 children of paretics, 66 were physically well and strong, 52 weakly and in a poor state of nutrition (21 rachitic), 6 afflicted with gross bodily deformities. Eight had prominent mental disorders (4 paretics), while 19 were mentally sound, 31 excitable and nervous, 4 quiet and retiring. Scholten found 36 out of 111 children of paretics suffering from nervous disturbances.

**SEX.** The cases of juvenile paretics reported have been about equally divided between the two sexes. In Thiry's<sup>12</sup> statistics of 62 cases there were 30 males and 32 females, and in our series of 23 cases the sexes were almost equally represented. It is interesting to contrast this uniform distribution in the two sexes to the disproportion in the adult form of the disease. In this period the male is represented among the paretic patients about 2 to 5 times as often as the female.

**AGE.** In Zappert's<sup>13</sup> case the patient was five years of age, which is the youngest one reported. Other cases have been reported occurring at subsequent ages up to late adolescence. Perhaps the most frequent age in which the disease appears is from eight to twelve years.

**Symptomatology.** The juvenile paretic may develop in a perfectly normal way until the symptoms of paresis gradually appear, or, what is more usual, the patient is inferior from infancy, both physically and mentally.

The initial symptom may be mental or physical. The earliest mental changes are referable to changes in the character and intelligence of the child; if it is already feeble minded it becomes more mentally deficient; if the child has shown a fair intelligence, there is added to a strange and unusual behavior a progressive dementia. The history is frequently obtained that the patient is becoming silly, forgetful, sometimes bad-tempered and does strange things, wandering away from home, aimlessly walking the streets, giving up occupation for no reason. The child may lose its affection for its parents, becomes taciturn, inactive, inattentive and irascible.

In adult paresis the most important psychic disturbances from a diagnostic standpoint are early uncertainty in grasp of time relations, weakness in memory, disorder of comprehension, intelligence defect, poor judgment, dulness of mood, emotional instability, and easily influenced behavior. Many of these early psychic disturbances are absent in the juvenile paretic. Moreover, delusions of a sexual nature and grandiose delusions of wealth, strength, and power, colored by events of the period rarely occur in the juvenile paretic except possibly in the adolescent period. The reason is that ambition and the sexual instincts do not become habitual passions dominating the will until after puberty. They are, therefore, not a content of consciousness at the age many juvenile paretics develop. However, Mott reports 1 case in which childish ideas of grandeur occurred and Kleinberger 5 cases.

There is considerably less of a distinction of clinical types in the juvenile paretic than in adult paresis. However, the agitated type may be seen in which there occur outbursts of excitement, or the child shows senseless crying, does not remain in bed, throws itself about, grasps at imaginary objects. Essentially the type of juvenile paretic is the simple demented. At the time one sees most of the cases they present the clinical picture of imbecility, which in a way corresponds to the third stage of the adult paretic with the somatic and spinal fluid picture of paresis.

*Somatic Symptoms.* The early symptoms of juvenile paresis may be physical, an apoplectiform or epileptiform seizure. Or, the first evidence may be symptoms referable to the motor apparatus such as stumbling, ataxia or incoördination movements.

Convulsions are very frequent in the course of juvenile paresis. They are mostly of an epileptic character and may be repeated day after day without any apparent after-effect. The somatic symptoms of juvenile paresis do not essentially differ from those seen in adult paretics except possibly symptoms referable to the motor apparatus. Motor symptoms appear earlier than in adults and

often are the conspicuous symptoms. In addition to the motor symptoms already mentioned there occurs early tremor of the hands, lips, tongue, and face; peculiar choreiform movements and at times characteristic chewing and sucking movements. Speech defect is usually present.

*The Pupils.* Pupillary abnormality constitutes an important somatic symptom of neurosyphilis. It usually appears early and is almost constantly present. In exceptional instances, however, the pupils may be normal in all forms of neurosyphilis, although this is less likely in paresis than in other forms of neurosyphilis. There is no characteristic pupillary abnormality of paresis. The pupils may be variable in size, although irregularity is of greater diagnostic import, they may be of the Argyll-Robertson type or reaction both to light and accommodation may be absent. Optic atrophy is more often present in juvenile paresis than in adult paresis, these cases usually presenting one or more symptoms of tabes, thus placing them in the tabo-paretic group. The combination of the two diseases occurs apparently more frequently than in adults.

*The Reflexes.* The reflexes are usually exaggerated with the presence of ankle clonus and the Babinski reflex. Sometimes a permanent dorsal flexion of the great toe results.

**Clinical Stigmata of Congenital Syphilis.** Clinical stigmata of congenital syphilis may or may not be present in juvenile paretics. Indeed, the majority of congenital syphilitics do not present the classical stigmata described by Hutchinson. However, in congenial syphilitics one is likely to find bone changes as seen in radiographic examination of the knees and long bones of the legs, or choroiditis as seen in ophthalmoscopic examination and auditory nerve involvement as elicited by Bárány's test.

**Pathology.** The most characteristic and constant pathology in adult paresis is a diffuse perivascular plasmocytosis and lymphocytosis and in relation to the small cortical vessels. A variable degree of meningeal plasmocytosis and lymphocytosis, granular ependymitis, parenchymatous atrophy, and gliosis are additional characteristic features of the pathology.

The neuropathology of juvenile paresis is essentially no different from that of the adult form. One of the early accounts of the pathology of juvenile paresis by Watson<sup>14</sup> which was published before the classical work of Nissl and Alzheimer on the pathology of adult paresis, gives descriptions that might be well used for the adult form.

**Course.** The course of juvenile paresis is from three to nine years, the average a little longer than it is in adults. Alzheimer places the average duration as four and a half years. Kraepelin records a case the duration of which was nine years. The prognosis of juvenile paresis is universally poor. Remissions are practically unheard of, and treatment seems to have no effect.

**"Preparetic" Congenital Syphilitics.** It is an important fact that congenital syphilitic children, with or without objective symptoms of neurosyphilis, sometimes show a spinal fluid finding characteristic of paresis. This is likewise observed in congenital syphilitics who are feeble-minded but neurologically normal. In the light of present knowledge the status of such patients cannot be stated definitely. It is thought that spinal fluid abnormalities precede for a number of years clinical evidence of neurosyphilis and that an abnormal spinal fluid typical of paresis represents the "preparetic" stage of the disease. However, it will require years of observation to properly interpret the significance of the paretic gold-curve in this class of case.

**Laboratory Diagnosis.** In view of the rarity of juvenile paresis as compared to the adult form of the disease, the laboratory picture of adult paresis is better known. It is reasonable to consider that the laboratory picture of the two diseases does not differ, at least it did not in the cases herein reported nor in the more recent ones reported in the literature.

**Discussion of Cases.** *Sex.* Of the 23 cases of juvenile paresis (see table), 11 were males and 12 were females.

*Age at Onset.* The age at time of the development of initial symptoms of paresis could not be determined accurately in all cases. As far as it could be determined, from the history, in 22 cases it ranged from three years (Case No. 12) to twenty-one years (Case No. 10). There was 1 patient in whom the initial symptoms appeared at the age of three, 4 patients at the age of five; 12 patients ranging from seven to twelve years of age; and 5 patients ranging from sixteen to twenty-one years. It is seen from the foregoing that in about 50 per cent of the patients, the initial symptoms of paresis appeared between the ages of seven and twelve years. In most cases the interval between initial symptoms and frank symptoms of the disease ranged from one to four years. In a few patients it was longer, five years in Case No. 16; seven years in Case No. 2.

*Age at Diagnosis.* The youngest patient was six years of age (Cases Nos. 12, 14); the oldest, twenty-four years of age (Case No. 3).

There were 5 patients ranging from age six to nine; 10 patients ranging from age twelve to sixteen; 5 patients ranging from age seventeen to nineteen; and 2 patients aged twenty-three and twenty-four years. In these 2 patients, although acquired syphilis could not be definitely excluded however, the history, the age of onset and in 1 Hutchinsonian teeth, supported the diagnosis of congenital rather than acquired syphilis.

*The Family History.* It was not possible to examine or to perform the Wassermann tests in the parents of all the cases of juvenile paresis. Of 12 mothers examined, 10 had definite evidence of syphilis; in 9 the Wassermann reaction was positive, the tenth had

TABLE I.

Case No.	Sex.	Age at examination.	Age at onset.	Family history.	Past history.	Mental symptoms.	Physical symptoms.	Wassermann.		Globulin.	Albumin.	Cells.	Gold-sol.
								Blood.	Spinal fluid.				
1	M.	18	..	Unknown	Unknown; always considered defective; picked up by police; confused and acting peculiarly. At 2 weeks, developed skin trouble with alopecia—continued 10 mos.; eyes weak from birth; walked and talked early; began to deteriorate mentally and physically at 5; eye trouble at 6 (probably interstitial keratitis); convulsions began at 8; attacks of blindness; hemiplegia of 6 weeks' duration at 8; following convulsions 2 mos. ago, has been blind. Always peculiar; wild; at reform school	Markedly defective mentally; euphoric; no delusions or hallucinations. Condition that of an idiot	Suggestive teeth; unequal, poorly reacting pupils; speech defect. Blind; dilated, unequal, non-reacting pupils; very active tendon reflexes; very unsteady on feet; speech indistinct; infantile development	+	+	+++	+++	108	Not performed.
2	M.	12	5	Father, 38; rheumatism, heart Mother, 31; healthy 1. Boy, 14; dull 2. Patient 3. } Boys; still-born 4. } 5. Boy, 6; well 6. Girl, dead at 2 of pneumonia				+	..	+++	+++	50	5554310000
3	M.	24	20 (?)	Father, dead, cause unknown Mother, living; Wass. negative 1. Girl; W.R. negative 2. Patient		Irritable, erratic and threatened to shoot sister and mother; idle, silly, demented Demented; memory shattered	Peg-shaped teeth; pupils stiff, unequal; tendon jerks absent; speech defect Dilated, stiff pupils; tendon reflex very active; speech defect	—	+	+++	+++	139	5555210000
4	F.	12	12	Father, unknown Mother, unknown 1. Patient, illegitimate	Bright, active child; went to 6th grade, then began to deteriorate; shock when 11			+	+	++	++	43	5555443210
5	M.	13	13	Father, W.R. + Mother, W.R. + 1. Patient	Healthy child; somewhat slow in schoolwork; 5 mos. before admission to hospital had a dizzy spell from which time his symptoms date	Hallucinated and deluded; memory defective; silly, irritable and uncontrollable	Saddle nose; rhagades about mouth; notched teeth; speech defect; unequal, irregular and stiff pupils; staggering gait	+	+	+	+	9	55555421000
6	F.	14	10	Father, 48; living; well; W.R. neg. Mother, 38; living; well; W.R. + 1. Sister, 16; juvenile parietic (Case No. 7) 2. Patient	No stigmata of congenital syphilis; symptoms began at age of 10 with drowsiness and headache; began to have spells when "she was unable to control her limbs," difficulty with gait progressive; deteriorated rapidly in last 6 mos.	Very much deteriorated girl; cries and screams, but does not talk; condition that of an idiot	Incisor teeth spaced and slightly notched; no other stigmata of congenital syphilis; speech defect; ataxic gait; tremors; pupils could not be examined	+	+	+++	+++	10	55555421000

No.	Sex	Age	History	Present Illness	Course	Prognosis	Remarks	Ref.
7	F.	16	Father, 48; living; well; W.R. neg. Mother, 38; living; well; W.R. + 1. Patient 2. Sister, 14; juvenile parietic (Case No. 6)	No stigmata of congenital syphilis; well until 12 yrs., when she had a shock, causing hemiplegia; at 14 had a second shock, causing hemiplegia of other side Patient was restless and difficult to manage; unable to get on in school; committed as feeble-minded when 7 yrs. of age; was healthy until 16, when she became irritable and began to dement	Retarded, irritable and deteriorating	.....	+	21
8	M.	9	Father, W.R. negative Mother, neg. W.R. on blood and sp. fl.; had had antisiphilitic treatment 1. Patient	Father living; well; W.R. neg. Mother dead—heart disease 1. Boy died at 4 yrs. of pneumonia 2. Patient 3. Age 17; W.R. negative 4. Age 15; W.R. negative 5. Age 12; W.R. negative 6. Age 6; W.R. negative	Feeble-minded; uncontrollable and apparently dementing	Pupils dilated and non-reacting to light or distance	+	42
9	F.	19	Father living; well; W.R. neg. Mother dead—heart disease 1. Boy died at 4 yrs. of pneumonia 2. Patient 3. Age 17; W.R. negative 4. Age 15; W.R. negative 5. Age 12; W.R. negative 6. Age 6; W.R. negative	Father living; well; W.R. neg. Mother dead—heart disease 1. Boy died at 4 yrs. of pneumonia 2. Patient 3. Age 17; W.R. negative 4. Age 15; W.R. negative 5. Age 12; W.R. negative 6. Age 6; W.R. negative	Memory poor; attention poor; demented; confused at times; outbreaks of anger; euphoric; at times depressed	Frontal headaches; pupils unequal, with sluggish reaction; tremors; incoördination in finer movements; speech defect	+	14
10	M.	23	Father, unknown Mother, unknown 1. Refused examination 2. Patient	At 21, became grandiose and excited; this lasted a short time, and then deterioration began Hypomanic	Unequal, irregular, Argyll-Robertson pupils; knee-jerks are absent; speech defect	Unequal, irregular, Argyll-Robertson pupils; knee-jerks are absent; speech defect	+	55
11	F.	12	Father, blood +, sp. fl. negative Mother, blood neg., sp. fl. neg. 1. Girl, W.R. neg. on blood 2. Patient 3. Boy, W.R. +, on blood, sp. fl. — 4. Boy, W.R. neg., on blood, sp. fl. — 5. Girl 6. Still-born	Perfectly well until he broke down in the Army in France; as a child, he had typical old-man appearance Precipitated by a fall	Quite demented; does not talk	Does not talk or walk	+	37
12	M.	6	Father, living, 43 } Not examined Mother, living, 34 } examined 1. Boy, 8, feeble-minded; not examined 2. Patient 3. Boy, 5 } Not examined 4. Girl, 3 } 5. Boy, 2 } 6. Miscarriage	Said to have been normal until 3; talked and walked; following a fall at 3 has been demented.	Does not talk or walk	Does not talk or walk	+	26
13	F.	9	Father, 36 } Not examined Mother, 36 } 1. Miscarriage 2. Patient 3. Miscarriage 4. Girl 5. Boy 6. } Miscarriages 7. } 8. }	Did well in school until third grade, then began to dement	Very much demented; does not talk; cries much of the time; unable to walk	Congenital amputation of toes and fingers; right pupil does not react	+	34



TABLE I.—(Continued).

Case No.	Sex.	Age at examination.	Age at onset.	Family history.	Past history.	Mental symptoms.	Physical symptoms.	Wassermann.		Globulin.	Albumin.	Cells.	Gold-sol.
								Blood.	Spinal fluid.				
14	F.	6	5	Father, dead; cause unknown; syphilitic. Mother, living; W.R. + 1. Boy, 16, living and well. Born before mother was infected. 2. Girl, 9, living and well. 3. Girl, 8, living and well; W.R. + 4. Patient 5. Girl, died at 9 weeks 6. Boy, 4; W.R. neg. Father, dead—accident Mother, living and well 1. Boy, 23 2. Boy, dead at 9 3. Patient 4. } Miscarriages 5. } 6. } 7. } 8. Boy, 11	Quite bright until accident at age of 5; then marked change in character and personality, with deterioration; walking becoming more and more difficult	Demented; irritable; restless	Spastic gait; exaggerated knee-jerks	+	+	+	+	..	1122100000
15	F.	13	11	1. Boy, 16, living and well 2. Girl, 9, living and well 3. Girl, 8, living and well; W.R. + 4. Patient 5. Girl, died at 9 weeks 6. Boy, 4; W.R. neg. Father, dead—accident Mother, living and well 1. Boy, 23 2. Boy, dead at 9 3. Patient 4. } Miscarriages 5. } 6. } 7. } 8. Boy, 11	Well and quite normal until 11, when she began to be nervous and irritable and then demented	Dementing; memory very poor; silly; cheerful	Right pupil greater than left; both irregular—right reacts slightly to light, left not at all; left knee-jerk more active than right	+	+	+	+	18	Not done.
16	F.	17	12	Father, dead, 48, accident Mother, dead, 45—heart disease 1. Girl, married, no children 2. Patient 3. Boy died in infancy 4. Girl; W.R. negative 5. Girl; W.R. negative Father, 37; migrainous Mother, 37 1. Boy, 10 2. Patient 3. Girl, 6 4. Boy, 4	Normal as a child; school from 6 to 12 in 7th grade; blindness began at 12; progressive, now complete; fainting spells began at 11; no convulsions	Demented; very grumpy; a great singer; to care for all orphans in the world; very euphoric	Optic atrophy; lively tendon reflexes and Hutchinsonian teeth	+	+	+	+	15	Not done.
17	F.	8	6	Father, 37; migrainous Mother, 37 1. Boy, 10 2. Patient 3. Girl, 6 4. Boy, 4	At 2 yrs. said to have had meningitis; improved; convulsions started at 3, time she had worms; syphilis diagnosed and arsenamine given; at 7 a right-sided paralysis given intraspinal injections without improvement	Excited; demented; untidy; memory poor	Unequal Argyll-Robertson pupils; speech defect; epileptiform seizures	+	+	+	+	35	Not done.
18	M.	19	17	Father, 42; neurosyphilis Mother, 41; general paresis 1. Patient 2. Boy, d. 20; ruptured aortic aneurysm 3. Boy, 19; W.R. neg.; achondroplasia 4. Boy, 17; W.R. neg.; caries of spine 5. Boy, 14; W.R. neg.; stigmata of congenital lues 6. } Still-births 7. } 8. }	8 months' child; healthy; went 1 yr. to high school; at 17 began to have difficulty in walking; speech defect appeared; became childish and had to be taken out of school	Demented; talks incoherently with speech defect; no delusions or hallucinations; spastic gait; square head and prominent frontal bosses	Argyll-Robertson pupils; speech defect; tendon reflexes	+	+	+	+	60	Not done.

19	M.	7	5 (?)	Father, dead; syphilis Mother, living; syphilitic 1. Child, d. 6; "meningitis" 2. Still-birth 3. Girl, d. 2 wks. 4. Miscarriage 5. Patient 6. Girl, 6; W.R. negative	Recognized as syphilitic at birth; treated by mercury pills; had fainting spells early in life; did not talk until 3; walked at 5 mos., but at 5 yrs. began to stumble; he began to deteriorate at this time	Restless; idiotic	Underdeveloped; glands in neck and groin; pupils unequal, irregular and stiff; completely deaf; difficulty in gait	+	+	++	++	++	44	5555431000
20	M.	15	10 (?)	Father, living; tabes Mother, living; 8th nerve palsy 1. Patient	Patient developed slowly; was considered feeble-minded; began to deteriorate mentally at about 10 yrs.; at 15, after being examined, had 2 shocks, causing quadriplegia; died a couple of weeks later	Imbecile type	Typical congenital syphilitic facies with Hutchinsonian teeth; pupils normal; speech defect; incoördinate	+	+	++	++	++	115	5555221000
21	F.	12	..	Father, living; paresis Mother, living; neurosyphilis 1. Patient 2. Boy, 10; feeble-minded; W. R. neg. 3. Boy, 8; W.R. blood +, sp. fl. neg. 4. Boy, 7 (mental age 3); W.R. blood + 5. Girl, 5 (mental age 3) W.R. blood neg. 6. Boy, 2½; W.R., blood doubtful 7. Boy, 8 mos.; not examined	Healthy; has always been dull and stupid	Feeble-minded; intelligence quotient, 48	Pupils do not react to light or accommodation	+	+	++	++	+	1	5555441000
22	M.	18	17	Father, dead at 62; cause unk. once; now negative 1. Boy, d. 11 mos.; ? diphtheria 2. Boy, d. 18 mos.; pneumonia 3. Boy, d. 22 yrs.; t.b. (convulsions in childhood) 4. Boy, d. 20 yrs.; pneumonia 5. Patient 6. Girl, 16; many bony lesions; gummatous 7. Still-birth 8. Girl, d. 14 mos.; meningitis 9. Abortion at 3 mos.	Normal, healthy, bright boy; no trouble until age of 17, when he was irrational, hallucinated and deluded	Dementing; silly; poor memory	Pupils small, irregular, Argyll-Robertson reaction; tendon reflexes exaggerated; tremors; speech defect	+	doubtful	++	++	++	127	Not done.
23	F.	7	5	Father, living; W.R. blood + Mother, living; W.R. blood + 1. Premature birth, 8 mos.; died 2. Still-birth 3. Patient	Normal development until 5 yrs. of age, then developed difficulty in walking; became silly, forgetful and gradually demented	Disoriented; resistive; comprehends very little; makes unintelligible sounds	Pupils unequal, irregular and react poorly to light; unable to stand alone; exaggerated tendon reflexes; ankle clonus; Babinski sign	+	+	+	..	+	240	Not done.

had antisyphilitic treatment before being seen by us. In only 2 was there no evidence of syphilis and the husband of 1 of these women had a positive Wassermann reaction. Unfortunately spinal fluid examinations were not made as a routine on the parents or siblings. However, neurosyphilis was found in the parents of 3 juvenile paretics. The mother of patient No. 18 had paresis, the father had neurosyphilis. The father of patient No. 21 had paresis and the mother had neurosyphilis. The father of patient No. 20 had tabes and the mother had eighth nerve palsy. The patients in Cases Nos. 6 and 7 were sisters, both being diagnosed as juvenile paresis.



FIG. 1.—Case No. 3. Juvenile paretic, aged twenty-four years; was always peculiar; wild; was at reform school; is irritable, erratic, threatened to shoot mother and sister; idle, silly and demented; pupils unequal and do not react to light or to accommodation; patellar reflexes absent; speech defect; Hutchinsonian teeth; Wassermann reaction—blood, negative; spinal fluid—cells 139; globulin, positive; Wassermann reaction, positive; gold-sol, 5555210000.

*The Siblings.* In 3 cases (Nos. 4, 5, 8) the patient was the only child. Of the remaining cases there was one or more brothers and sisters. It was not possible to examine and to perform the Wassermann test on all the siblings. Of the brothers and sisters in which it was possible to perform the test, the results were variable. The test was negative or positive in all or negative in some and positive in others.

It is of interest to note that in the series there were two sisters (Cases Nos. 6 and 7) who were paretics. The father and mother of these patients were living and well, the father's blood Wassermann

was negative, the mother positive. There were no other children nor any miscarriages or stillbirths.

In Case No. 18, as pointed out in the foregoing, the parents had neurosyphilis, the mother was a paretic, the patient (a juvenile paretic) was the eldest of 5 children, of these children, 1 died at the age of twenty of a ruptured aortic aneurysm, 1 had chondroplasia, 1 had caries of the spine, and the remaining 1 presented stigmata of congenital syphilis. The Wassermann tests of these siblings were all negative. The foregoing furnishes instances of Fournier's dys-



FIG. 2.—Case No. 4. Photomicrograph showing meningeal infiltration.

trophies of congenital syphilis. Following the birth of the fifth child there were three successive stillbirths, an exception to the well-known law of Kassowitz.

In Case No. 20, the father was a tabetic, the mother had an eighth nerve palsy of syphilitic origin. Their only child was a paretic.

In Case No. 21, the father had paresis, the mother neurosyphilis, there were 7 living children, the oldest a juvenile paretic. Two others had a positive blood Wassermann reaction and most of them were feeble-minded. This case, and perhaps Cases Nos. 20, 18, 6

and 7 lend support to the existence of a neurotropic strain of spirochete.

*Symptomatology.* In the discussion of the symptomatology of the 23 cases of juvenile paresis, there is little to be added here which has not been already mentioned in the text. In some of the cases the patient developed normally up to a certain period and then developed mental and physical symptoms. The mental symp-



FIG. 3.—Case No. 19. Juvenile paretic, aged seven years; father and mother syphilitic; one other child living whose Wassermann reaction of the blood negative; has been treated since birth with mercury; fainting spells early in life; began to stumble when five years of age and at about this time began to deteriorate mentally; is restless and idiotic; pupils unequal, irregular and do not react to light or to accommodation; deaf; difficulty in gait; no stigmata of congenital syphilis. Wassermann reaction: blood, positive. Spinal fluid: cells 44; globulin, positive; Wassermann reaction, positive; gold-sol: 5555431000.

toms were those of a beginning dementia which was progressive. Of the physical symptoms epileptiform seizures were conspicuous, being present in 8 of the 23 cases, less frequently present were symptoms referable to the motor apparatus. In 4 of the patients there was a precedent attack of hemiplegia and 2 patients had optic atrophy, conditions which are rarely associated with paresis of the adult type.

At the time the patients were first seen most of them presented

the picture of imbecility, they were considerably demented with periods of excitement. Delusions of grandeur were absent in the younger patients but were present in 2 of the older patients, aged seventeen and twenty-three years respectively (Cases Nos. 16 and 10).

It will be noted that in 2 patients (Cases Nos. 11 and 12) initial symptoms of paresis appeared after trauma. The influence of head injuries in the development of paresis has been pointed out by many writers and recently by one of us (J. V. K.).<sup>1</sup>



FIG. 4.—Case No. 20. Juvenile paretic; aged fifteen years; father a tabetic; mother has an eight nerve palsy; patient the only child; developed slowly and was considered feeble-minded; mental deterioration began at about the age of ten years; is imbecilic; pupils normal; speech defect, incoördinate; congenital syphilitic facies, frontal bosses, saddle nose, Hutchinsonian teeth, rhagades; Wassermann reaction: blood, positive. Spinal fluid: cells 115; globulin, positive; Wassermann reaction: positive; gold-sol: 5555221000. Developed quadruplegia, died soon after.

*Objective Symptoms.* All but one of the patients presented pupillary abnormality. As in paresis of adults, no characteristic form of pupillary abnormality was present. The pupils were unequal or irregular, reacted sluggish to light, or reacted neither to light or accommodation, or, were of the Argyll-Robertson type. It is of interest to note that in 1 patient (Case No. 20) the pupils were normal. Although pupillary abnormality is the most frequent clinical sign of neurosyphilis, in exceptional cases, even in paresis, it may be absent. We have seen cases of paresis in adults in which the pupils were normal.

<sup>1</sup> Syphilis and Trauma. The Workmen's Compensation Act. The Industrial Physician and the Syphilitic Employee, Jour. Am. Med. Assn., 1922, 78, 1029.

The reflexes were exaggerated in almost all of the 20 patients and absent in only a few of the patients. Only a few of the patients presented stigmata of congenital syphilis, which consisted principally, if not solely, of Hutchinsonian teeth. The teeth in others were suspicious but not typical of Hutchinson's type.

*Laboratory Tests.* The result of the Wassermann test of the blood and spinal fluid and other tests of the spinal fluid were very similar to what is present in paresis of the adult type.

The blood Wassermann was positive in 22 of the 23 cases and the spinal fluid Wassermann was positive in all of the cases. In the spinal fluid a positive Wassermann test in as small amount as 0.1 cc was the uniform finding.

A cell count was not recorded in 1 case. In the remaining 22 cases the smallest number of lymphocytes was 1 per cmm, and the largest number was 240 per cmm.

The lymphocytes ranged from 9 to 26 per cmm in 8 cases; from 34 to 60 per cmm in 8 cases and more than 100 per cmm in 5 cases.

The gold-sol was performed in 16 cases, the paretic curve was present in all but 1 of these cases. In Case No. 14 in which the paretic curve was not present, the diagnosis of paresis was justified from the mental symptoms. In the 7 cases in which the gold-sol was not performed, the diagnosis of paresis was justified from the clinical picture, other tests of the spinal fluid in these cases were positive.

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## A CASE OF MENINGOCOCCIC MENINGITIS FOLLOWING HEAD INJURY.

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ALTHOUGH it is recognized that such head injuries as penetrating wounds and compound fractures of the skull play an important role in the production of the suppurative meningitides due to various microorganisms, well-authenticated cases of meningococcic meningitis following trauma to the head are not common.

Parker,<sup>1</sup> in 1881, described the autopsy findings on two children, aged two and three years respectively, dying with cerebrospinal meningitis. One had fallen out of bed, the other downstairs. In both the symptoms of meningeal irritation began in two or three days after the fall. The younger child died in twenty-three days, the older in forty-three days. A heavy, fibrinopurulent exudate was encountered at the base of the brain at autopsy but no fracture of the cranial bones could be demonstrated. Inasmuch as the meningococcus was not described by Weichselbaum until six years later, the infection was not referred to in these terms. It seems possible, however, that the meningitis in both instances was of meningococcal origin.

In 1905, Busi<sup>2</sup> told of a man, aged twenty-five years, who sustained a head injury when thrown to the ground in a fight. Epistaxis commenced immediately and, within twenty-four hours, there was evidence of meningeal irritation. After a rapidly progressive course, the man died in four days. At necropsy, although no fracture of the skull was found, a copious fibrinopurulent exudate covered the brain surfaces. Intracellular Gram-negative diplococci were seen in the smears from the exudate.

None of these 3 cases showed skull fracture. On the other hand, Lenhartz<sup>3</sup> reported the instance of meningococcic meningitis where a fracture of the skull preceded the inflammation. Lindstrom,<sup>4</sup> too, recounted the findings of a twenty-three-year-old farmer who suffered a penetrating wound of the right orbit, attended by epistaxis. Two days later headache, vomiting, and rigidity of the neck appeared, death ensuing in six days, after a trephine operation of the frontal and ethmoidal cells. Postmortem examination revealed a well-established meningococcic meningitis. As the patient's father had died six months previously of the same disease, the



author evidently felt that the infection extended from the nasopharynx into the cranial cavity.

More recently, in 1921, Kalb<sup>5</sup> cited an attenuated case of meningococcic meningitis with recovery, occurring a few days after an injury to the temple in a middle-aged man. At the time of trauma there was profuse bleeding from the ear and concussion of the brain, although no fracture could be found. The author discussed the possibility of extension of the infection through the auditory canal, from the nasopharynx or by way of the blood stream, but favored direct extension as the more likely route. He also mentioned a case of meningitis due to the meningococcus described by Imhofer, where the meningitis followed a penetrating wound of the neck.

Dr. E. B. Krumbhaar<sup>15</sup> has called our attention to a hitherto unpublished case which he encountered in a base hospital in France. A man, with a gunshot wound of the lumbar and sacral spine and signs of meningitis, gave a pure culture of meningococcus by spinal puncture. At autopsy various organisms (staphylococcus, streptococcus, etc.) were cultivated from the dirty wound which involved the sacrum and spinal cord but which remained fairly well localized. After an intermediate normal area, another typical meningitic area was reached from which meningococcus was again cultivated. Dr. Krumbhaar was inclined to believe that the man was developing meningococcic meningitis when injured, although he countenances the possibility that it may have been induced by the injury. Realizing certain analogies between this case and the one we have encountered, Dr. Krumbhaar very kindly forwarded the above data to us.

As can be seen, the literature is not replete with instances of post-traumatic-meningococcic meningitis. For this reason it is the object of this communication to report the findings of a case which, in certain ways, corresponds to some of those previously recorded, as well as presenting several features confirming similar infections produced experimentally, and observed clinically after lumbar puncture by Wegeforth and his co-workers.

The patient, a boy aged twelve years, was admitted to the hospital in a semi-comatose state with a history of having injured his head a few hours previously when thrown from a hay wagon against a telegraph pole. Examination revealed a contusion of the scalp over the left lower parietal region and a moderate epistaxis. At this time all other findings were negative, and the temperature, pulse, respiration and blood-pressure were normal. Next morning, the lad, having partially recovered from his lethargy, complained of a headache, nausea, and vomited several times. The temperature fell to 97.6° F., the pulse to 68, but the blood-pressure remained the same (120/80). The constant occipital headache increased in severity, but no roentgenologic evidence of skull fracture could be demonstrated. At four o'clock in the afternoon, about thirty

hours after the injury, the temperature rose to 99.2° F., continuing its ascent in a step-like fashion until four days after the accident it was 103.4° F. During this period the pulse ranged from 80 to 100, but the leukocyte count never exceeded 7500. Although there were no convincing signs of increased intracranial pressure, the intractable headache, the febrile state, a beginning rigidity of the neck, a positive Kernig's sign and an increasing apathy indicated meningeal irritation, so that a lumbar puncture was deemed justifiable.

Access to the spinal canal was accomplished without difficulty and a turbid, bloody, cerebrospinal fluid, under increased pressure, was obtained. The leukocytes, most of which were polymorphonuclear, numbered 4500 per cm. and the erythrocytes, many of which were crenated, totalled 6000 per cm. Direct smears of the centrifuged fluid, stained by Gram's method, showed many relatively large, pink, biscuit-shaped, intracellular and extracellular diplococci. These grew on human blood agar plates as uniformly round, moist translucent colonies, which after twenty-four hours incubation at 37.5° C were from 1.5 to 2 mm. in diameter, gradually increasing in size and opacity in three or four days. These organisms fermented dextrose and maltose, but not saccharose, in serum broth. No serological determinations were made and there was no record of a blood culture on the patient.

Immediately following the lumbar puncture the boy was removed to the Municipal Hospital where, after intravenous and intraspinal administration of antimeningococcic serum, the cerebrospinal fluid rapidly cleared up, being sterile in forty-eight hours and of normal cytology in eight days. Pursuant to an uneventful recovery, he was discharged as well sixteen days after the injury. The clinical diagnosis was concussion of the brain and cerebrospinal meningitis (meningococcic).

From its incipency, the disease in this instance was essentially one of meningeal involvement, the manifestations of profound sepsis being absent. At no time was a cutaneous eruption apparent. Notwithstanding, a blood culture in the early hours of the malady might have proven very instructive. While it will never be known whether or not a fracture of the skull or organic cerebral traumatization resulted from the injury, clinically there was but little evidence that such was the case. On the other hand it is hard to believe that the blood entered the spinal fluid coincidently with the lumbar puncture. Moreover, the crenation of the red corpuscles would suggest that they had been present in the fluid for some time. In any event, it is known that a head injury of no mean consequence occurred in a boy, who had been previously healthy, who had not been exposed to a traceable case of cerebrospinal fever, and in whom signs of meningeal irritation began within thirty hours after an injury which occasioned a *commotio cerebri* and, in all prob-

ability, minute lacerations of the brain, or rupture of cerebral or meningeal capillaries, if not a slight fracture of a cranial bone.

While it is not to be denied that the chain of evidence as to whether or not the trauma was directly responsible for the localization of the meningococcus on the meninges is incomplete, the data in this case would seem to indicate that the trauma did exert a predisposing influence at least in the production of the meningitis, although it is regrettable that postnasopharyngeal and blood cultures were not available. Had both of these been positive for meningococci, one could justifiably assume that the bacteria gained entrance to the blood stream through a broken nasopharyngeal mucous membrane and thence were borne to the meninges by the hematogenous route.

That there are nasopharyngeal carriers of meningococci is well established, although it is logical to expect that few carriers should develop cerebrospinal fever. However, Flack<sup>6</sup> reports 5 cases developing among carriers in from one to forty days after isolation. In addition, no constant relationship has ever been established between the carrier state and active cerebrospinal meningitis. As Leake<sup>7</sup> says, in a disease whose degree of infectivity may be so low as in this one, the period of incubation is variable and uncertain, although there is evidence which places the usual incubation period at from one to five days.

Again, clinically, the relationship between meningococcemia and meningeal localization is variable. Although Duval<sup>8</sup> maintained that no authenticated cases were on record, in which the meningococcus had produced lesions outside the meninges in the absence of a preëxisting meningitis, several cases, notably those of Andrews,<sup>9</sup> Liebermeister,<sup>10</sup> Bovaird,<sup>11</sup> Cecil and Soper,<sup>12</sup> Bray,<sup>13</sup> Anderson,<sup>14</sup> Marino,<sup>16</sup> Findlay,<sup>17</sup> Monziols and Loiseleur,<sup>18</sup> and Bloedorn,<sup>19</sup> exhibited meningococcal bacteremias where there was no clinical evidence of meningeal involvement.

Since 1898, when Gwyn<sup>20</sup> reported a case, many instances where the meningitis has been preceded by the presence of meningococci in the blood stream have appeared in the literature. In this regard, Elser<sup>21</sup> found this bacterium in the blood stream in 10 of 41 cases, and Baeslack<sup>22</sup> in 36.3 per cent of 25 cases. Herrick<sup>23</sup> believes that epidemic meningitis is preceded by a stage, averaging forty-eight hours, in which evidence of a generalized infection occurs, whereas Sainton and Bosquet<sup>24</sup> state that meningococcemia as well as meningitis may be of such attenuated form as to be unrecognizable. Surely the localization of a disease like cerebrospinal fever, which can be so variable in its pathogenesis, so inconstant in its laboratory findings, and so protean in its clinical manifestations might well be influenced by a head injury.

In fact, it has not been long since the teachings of Westenhoeffer<sup>25</sup> have lost caste. While admitting a dual pathway, hematogenous

and lymphatic, of infection for the meninges, Westenhoeffer felt that the causative bacteria travelled directly from the nasopharynx and accessory sinuses along the nerves and lymph channels. Netter<sup>26</sup> was one of the first to appreciate the importance of the hematogenous route in meningitis. He produced a localization of pneumococci, given intrapulmonically to animals, by cauterization of the meninges after trephine. Since Elser and Huntoon<sup>27</sup> indicated that the weight of evidence up to that time (1909) pointed to the hematogenous origin of meningococcic meningitis, the idea of direct extension from the upper respiratory passages has lost considerable support, and the present conception that the meningococci are borne to the meninges through the blood stream is generally admitted.

Equally interesting and significant are the experimental findings of Weed, Wegeforth, Ayer and Felton,<sup>28</sup> who produced a meningitis in cats, by releasing the cerebrospinal fluid by means of occipito-atlantoid or lumbar puncture after an artificial bacteriemia, using *B. lactis aërogenes*, and later *B. pyocyaneus*, and *B. paratyphosus* *B.* as well as *Streptococcus* in rabbits. Full advantage was taken of these observations by Wegeforth and Latham,<sup>29</sup> who felt that lumbar puncture was directly responsible for the production of 5 human cases of meningitis (2 due to pneumococcus and 3 to meningococcus) in individuals who were harboring these organisms in their blood streams. They believed that the localization of the microorganisms on the meninges depended in part on physical factors involving the distribution of pressure relations within the cranial cavity.

In this regard mention should be made of those instances of "serous meningitis" which occasionally follow head injuries or lumbar punctures and in which the excitant would appear to be purely a mechanical irritation. Lemon<sup>30</sup> reports 2 such cases following trauma to the head, both of which recovered after decompression. It is not difficult to conceive that, if organisms had been circulating in the blood current of the cases when the meningeal changes were occurring, a purulent meningitis might have resulted. Further evidence that mechanical influences may predispose to a localization of bacteria on the meninges can be found in the case, as described by Tantzén,<sup>31</sup> in which a woman, aged forty-seven years, developed a meningococcic meningitis within four days, following an attack of cerebral hemorrhage, occasioning an apoplectic seizure.

With these facts at hand, it would seem highly probably that, in many of the reported cases, including our own, the factors attendant upon the altered pressure relationships within the calvarium, as suggested by the experimental evidence of several investigators, predisposed to the localization of the microorganisms on the meninges—even if the disturbed relations were produced in different ways.

It is our belief that, in the case herein reported, the meningococci entered the vascular system through a rent in the nasopharyngeal mucosa, which was caused by the injury and indicated, clinically, by epistaxis; that, owing to the disturbed intracranial conditions, resulting from the same injury, the meningococci found a favorable pabulum for proliferation on the meninges, by virtue not only of their inherent qualities but also of a resultant *locus minoris resistentiæ*, and that, in the present status of our knowledge of the subject, the wonder is not that these cases do occur, but that they are not encountered more frequently.

**Conclusions.** An instance of meningococcic meningitis with recovery occurring in a boy of twelve and beginning within thirty hours after an injury to the head, producing *commotio cerebri* and probably minute lacerations of the brain and rupture of intracranial capillaries, is reported.

While it is possible that the occurrence of the meningitis and the trauma were coincidental, nevertheless the evidence indicates that the injury predisposed to the meningeal localization of the bacteria, which could have gained entrance readily to the blood stream through the injured nasopharyngeal lining, from whence they were carried, hematogenously, within a skull where the pressure relations had been disturbed, where a *locus minoris resistentiæ* had been produced, and where rupture of capillaries, in all probability, had occurred.

The case is analogous, in many ways, to both the experimental findings and clinical observations of others.

With the incompleteness in the chain of evidence, this case, even if our interpretation is correct, does not contribute materially to our knowledge of the epidemiology of sporadic cases of cerebrospinal meningitis, but it should serve as a text to admonish alertness in observing head injuries carefully with the idea of early recognition of a possible meningococcic meningitis.

We acknowledge with gratitude our indebtedness to Dr. H. H. Donaldson and F. H. Rimer for the clinical records and to Dr. A. G. Sanblad for the translation of the article by Lindstrom.

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## THE PULMONARY SEGMENT REFLEXES.

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HENRY HEAD and MACKENZIE were the first to describe the segmental reference of pain in visceral disease. Pottenger has emphasized the importance of trophic changes and hyperalgesia in tuberculosis of the lungs. Head believed that he could determine the location of the lesion in the lung from the area of hyperalgesia. Pottenger, from the special character of his material, which usually has the apices of the lungs affected, attributed the reflexes to toxins from underlying lesions affecting the nerves.

In the strictest sense segment reflexes involve more than segments of the spinal cord, as they are in part conditioned by impulses from the brain. This is beautifully illustrated by a hemiplegic patient with asthma. During attacks of asthma there is less hyperalgesia and muscle tonus on the paralyzed side; on that side the expiratory excursions are wider and the physical signs are less intense. In the absence of asthma, respiratory excursions are less on the paralyzed side, as is usual. Disturbances of breathing and of other motor functions, have frequently been noticed as a sequel of encephalitis lethargica. Inspiration and expiration are uncoordinated so that tonic or clonic contractions of either inspiratory or expiratory group of muscles result. Sometimes this causes grotesque contortion. That the regulation of muscle tonus is a midbrain function has been shown by Sherrington and by Magnus and De Kleijn. Recently Pike and Coombs have reviewed the

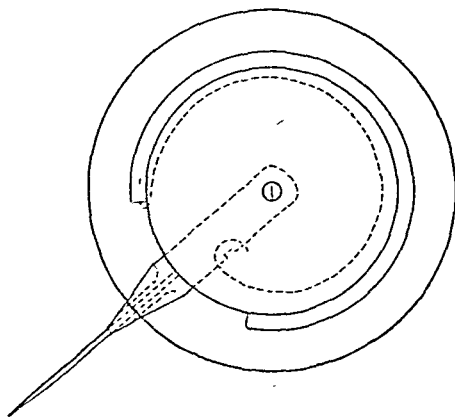
evidence on this point. Midbrain pressure is associated with stertorous breathing as a manifestation of increased inspiratory tone. These reflexes are designated *segment* reflexes because the peripheral response has a segmental distribution corresponding to the embryonic segmental origin of the organs involved. The afferent pathway is through sympathetic fibers in the vagus and the phrenic nerves.

We have not found segment reflexes as the result of high fever, as Head believed, unless it resulted from distention of an organ in consequence of congestion. We did not find it in a large number of cases of typhoid or scarlet fever examined, unless there was also distensible pressure in a viscus, as revealed by other physical signs.

It has been shown that distention in a viscus is reflected into the dermatome and myotome of the corresponding segment level and may spread to adjacent segments. The primitive reflex was probably in response to a bolus of food in the alimentary tube or to a mass of blood in the vascular tube. It is protopathic and is manifested by hyperalgesia, hyperthermesthesia, increased pilosensory irritability and increased muscle tone. The nodal character of the spinal distribution is clearly indicated, in the hyperalgesic area, by the reaction to stimulation as the margin of each segment is passed.

We have tested hyperalgesia by Mackenzie's method of dragging a sharp steel pin over the skin. The edges of the hyperalgesic zones in acute disease are found quite definitely and the patients complain of cutting or burning sensations and wince. At times we have used a weighted rod with a sharp point so as to eliminate the possibility of varying pressure.\* We have tested the patient without looking at the areas and asked an assistant to mark them. The constancy of the locations has been definite.

Hyperthermesthesia has been elicited with test tubes containing water heated to 45° C., or cooled below 10° C. Increased muscle



\* The author also employs this simple algometer designed by Edmund Bat-chelder. The tension of the piano-wire spring secures equal pressure because any change is indicated on the dial.

tone was elicited by pressure and revealed by tenderness, posture or displacement of viscera, as in the case of the diaphragm and also by changes in vital capacity. Atrophy of muscle from excessive tone is another evidence of these changes.

In pulmonary disease there are two distinct groups of segments involved. The cephalad group extends from the third cervical to the second thoracic, thus including the upper extremity. The caudad group consists of and usually involves the seventh thoracic and adjacent segments. At times the entire segment is not involved but only a maximum area as described by Head. Usually there are coincident sensory, muscular and trophic disturbances which may be equally involved, though this is not always the case. At times the intensity of the cutaneous reaction has been disproportionately large, or disproportionately small compared with the muscular disturbance from the corresponding segment.

The peripheral segmental reference has an embryonic basis. The lung is the only organ in the body whose vessels arise from a distant anlage, which is separated by a number of somites from the point where the viscus itself takes origin. This unique embryonic plan gives rise to a number of distinctive clinical correlations.

The cephalad representation corresponds to the development of the lung bud which becomes the visceral portion of the lung. In the fourth or fifth week of embryonic life (5 mm. embryo) the lung bud appears as an outgrowth on the anterior surface of the gut, at the level of the third cervical segment, which corresponds with the sixth somite. At this time the heart is in the neck and is still a branchial organ. The diaphragm, which at this time consists solely of the transverse septum, has not travelled into the abdomen to its ultimate site, dragging the phrenic nerves with it as it progresses. The migration of the diaphragm downward, may be traced in embryos of increasing length, until in time, the heart occupies its ultimate position in the thorax. The septum transversum, having traversed the thorax, finally approaches the eighth thoracic vertebra. The lung buds develop laterally to the heart, but mesial to the primitive pleuras, which have not yet become separated from the peritoneal coelom.

It was formerly taught that the pulmonary artery was an outgrowth from the sixth dorso-ventral aortic arch and accompanied the lung bud in its downward migration. Until recently it was believed that there was no embryonic plan for the development of the vascular system, but that vessels followed organs as the need for them arose. That view is no longer entertained by anatomists, who have found that a phyletic plan underlies the growth of veins and arteries, just as it does for the nervous system. Huntington and also Brown have recently shown that the pulmonary vascular bed develops from the post-branchial plexus into which the pulmonary bud advances. The post-branchial plexus represents aortic



arches lying caudad to the sixth, which do not persist in higher mammalian forms.\* This vascular bed, formed from these primitive arches, is a relic of some primitive vertebral type in which the entire gut participated in respiratory exchange. In the 7 mm. embryo the post-branchial plexus joins the sixth aortic arch, thus ultimately reaching the heart. The observed anomalies in the anatomy of the pulmonary arteries and veins support this view of their embryonic derivation. This caudad origin of the pulmonary vascular bed accounts for the lower thoracic segment representation from the lung. It is obviously vascular and I have so designated it.

We have then, two groups of pulmonary segment reflexes, a cephalad or *visceral* and a caudad or *vascular* group.

The spinal dermatomes or Head zones are frequently illustrated; tabulations of the myotomes are less well known but are given by Bing in his compendium. The location and involvement of the vascular and the visceral areas postulated, are readily grasped from such diagrams. It is apparent that muscles involved in ordinary diaphragmatic respiration rise from the third cervical segment and also that the intercostal muscles and the other muscles involved in thoracic breathing, arise from the seventh thoracic, as well as adjacent segments. The so-called accessory muscles of respiration are innervated by the same segments as are involved in the heightened cutaneous sensibility. The sternomastoid muscles are supplied by the spinal accessory nerves, which have a cervical origin extending to the seventh segment.

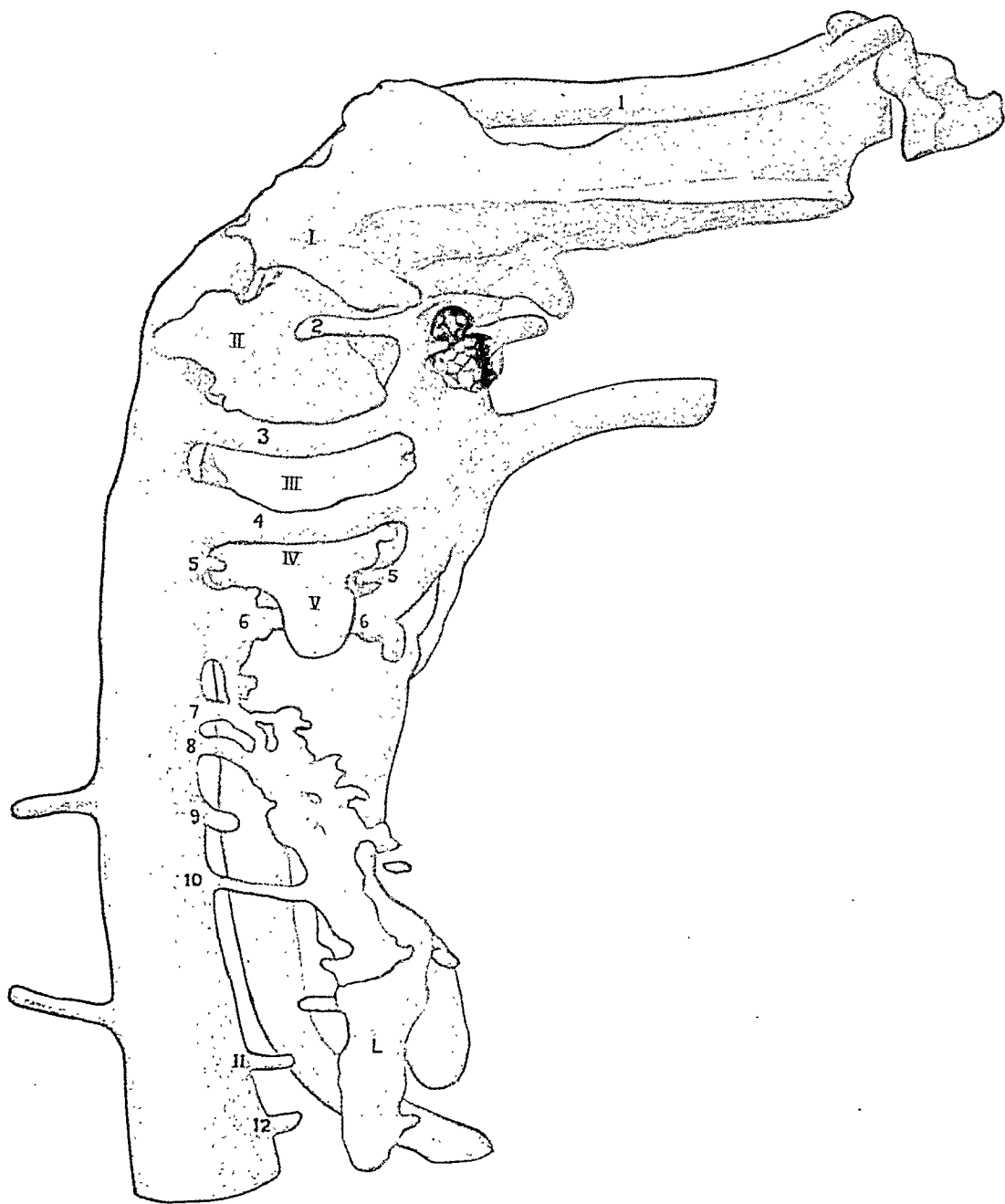
It is noteworthy that both visceral and vascular segment groups innervate muscles of inspiration. The expiratory muscles are innervated by a segment group which is still more caudad.

The visceral origin of the cephalad group of reflexes is shown by their appearance simultaneously with lesions of the lung, as in bronchitis, pneumonia, either lobar or lobular, tuberculosis, and in laryngeal or bronchial diphtheria.

The vascular or caudad reflex may disappear or appear independently under certain conditions, as in asthma. Depending upon whether the visceral or the vascular reflexes predominate, we obtain a cephalad or caudad type of emphysema. Tendeloo pictured these two types of pulmonary emphysema, but did not explain their mechanism. The cephalad or visceral group may be present in the absence of the vascular group, in diphtheria, involving the trachea or bronchi and in membranous bronchitis, in abscess of the lung after great emaciation and in pulmonary tuberculosis with wasting.

Several other groups of cases offer clinical evidence in favor of the view that the seventh thoracic segment represents the vessels of the lungs and that hyperalgesia and increased muscle tone appear as a result of distensile pressure in the pulmonary vascular bed.

\* Plate reproduced from the Anatomical Record by the courtesy of Professor George S. Huntington.





When there is passive congestion of the lungs, there is always present seventh thoracic hyperalgesia, which disappears when the congestion is relieved. This relief of distensile pressure may follow reduction of the blood mass, as the result of bleeding, or the reduction of the fluid intake, as by a Karell diet, or as the result of improvement in the peripheral and pulmonary circulation from rest in bed and the administration of digitalis. Coincident with the improvement, there is also a diminution of the muscle spasm of the segments involved. This is manifested among other ways, by the increase in vital capacity. Peabody and the Harvard school especially, have measured the latter phenomenon.

As the result of depletion of the blood mass, the segment tone diminishes, as I have been able to demonstrate in the donor, graphically, during a transfusion. In a group of adult measles cases observed from the beginning to the end of the attack, at Willard Parker Hospital, hyperalgesia involving the cephalad and the caudad group of segments appeared and again disappeared with the clearing of the pulmonary congestion and bronchitis. As the result of the marked loss in body mass during measles, the vascular hyperalgesia, in cases uncomplicated by pneumonia, usually disappears before the visceral segments have cleared up. In pneumonias the visceral and vascular zones are very prominent and come on coincidentally with the onset of the pulmonary lesion. In influenzal pneumonia there is marked congestion, so that the reactions from the vascular or caudad segments predominate. Due to congestion there is marked inelasticity of the lungs; in the presence of resulting intense reflex spasm, a characteristic emphysema of their margins and occasionally rupture of the lungs there, may occur.

Another group of cases which is especially instructive are the acute asthmatics. In these patients the onset of the typical attack is coincident with the development of marked vascular hyperalgesia and marked increase in tone of the muscles innervated from the caudad segments, as shown by the very great diminution of vital capacity. The hyperalgesia and the muscle spasm disappear about six minutes after the hypodermic administration of adrenalin. It may also disappear with benzyl benzoate, or a dose of morphine and atropine. Patients having asthma, associated with bronchitis show hyperalgesia and spasm of the visceral segments as well. These are unaffected by adrenalin. This reflex disappears with the healing of the lesion.

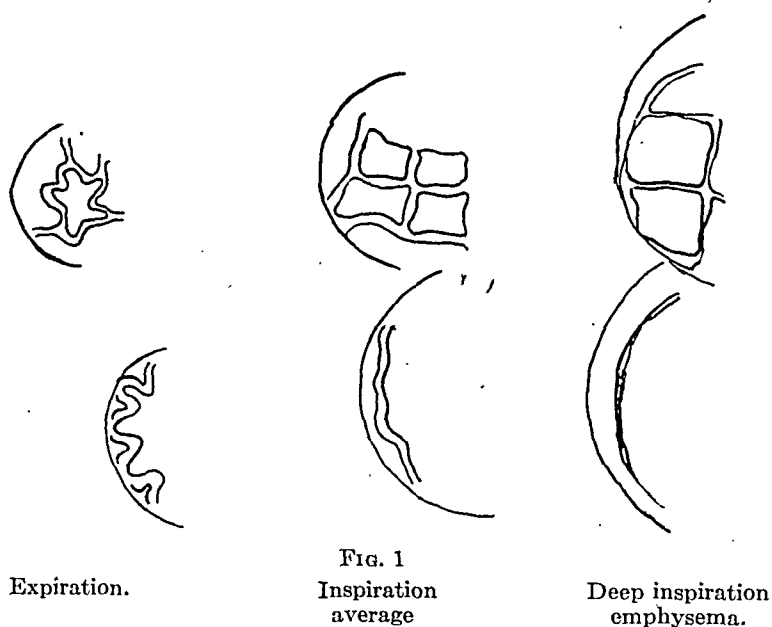
Let me narrate my observations on a patient who is subject to three different types of asthma. J. L. is aged twenty-one years. Since he was ten he has suffered from egg sensitization, with resultant acute attacks of asthma. For two years he has also suffered from attacks which are due to ethmoidal infection, with consequent bronchitis. In November, 1920, he came to me with an attack which was induced by eating ice cream containing egg. At that

time hyperalgesia was limited to the seventh thoracic segment, or solely vascular. His vital capacity during the attack was 996 cc per meter of surface. Six minutes after the hypodermic administration of 10 minims of adrenalin, the hyperalgesia disappeared and his vital capacity was increased to 2160 cc. After this administration of adrenalin, hyperalgesia involving the ninth thoracic segment appeared. In a recent attack, on October 20, due to an infection of the head and chest, there was marked hyperalgesia of the third and fourth segments and also of the seventh and ninth segments. Before adrenalin was administered his vital capacity was 2225 cc per meter of surface. After administering adrenalin the seventh thoracic segment hyperalgesia disappeared and his vital capacity became 2640 cc per meter of surface. The visceral hyperalgesia was unaffected. On November 5, after treatment with vaccines, all the hyperalgeias had disappeared and his vital capacity had increased to upward of 3000 cc. The change in the shape of this patient's chest during and after an attack is striking. Another type of attack also associated with bronchitis occurred on December 30. There was tightness of the chest and apparently this occurred without inspiratory muscular spasm because the chest was not expanded. Hyperalgesia was marked over the third and fourth cervical segments. There was no seventh thoracic hyperalgesia. Both inspiration and expiration were difficult. The vital capacity was 1560 cc per meter of surface, before adrenalin and 3209 cc six minutes after  $\frac{1}{2}$  cc of 1:1000 solution had been given hypodermically. In this case the bronchial muscles were relaxed by the drug and expansion of the lungs permitted. When the adrenalin effect wore off, benzyl benzoate was efficient in maintaining an expansile condition of the viscus.

The mechanism of the action of adrenalin in asthma is thought to be due to a specific relaxation of the bronchial muscles when they are contracted. In this connection it may be remarked that the contraction of the bronchial muscle is not sufficient to impede the exit of air, as is frequently believed. It certainly could not impede the exit of air, without impeding its entrance as well. Their contraction does, however, definitely interfere with the ability of the bronchial tree to be stretched.

In ordinary respiration the alveolar capillaries form a very tortuous network projecting into the alveoli. During expiration the tortuosity of the capillaries is increased. In inspiration the capillaries become straightened. In extreme inspiration the capillaries are thinned and compressed. Tendeloo has shown that the resistance to fluid flow through tortuous capillaries is greater than through straight capillary tubes of the same diameter. When the capillaries are compressed the resistance increases with the narrowing. As the result of expiration the more tortuous condition of the capillaries causes increased resistance and reflexly increases the tonus of the

muscles innervated by the segment which is stimulated. In deep inspiration the resistance is increased because the capillaries, though straight, are more tenuous (Fig. 1). With each increment in the resistance, there is an increase in the reflex inspiratory tonus, until the tonic spasm becomes extreme. Relief is obtained either as the result of carbon dioxide accumulation, by which the activity of the centers is depressed, or by therapy directed either against the spasm of the bronchi, the blood stasis or the reflex irritability. Release of the spasm of the bronchi permits a more general expansion of the lung, with less tension in the alveolar portion. The improved circulation brings about diminution of the lung volume, because, as stated, there is diminished reflex spasm with decrease of pulmonary vascular tension.



After great exertion, as from running, there is a diminution of vital capacity and pain in the sides, but no bronchial spasm. This physiological congestion accounts for increased vital capacity following exercise. The increased inspiratory muscle tone is a conservative mechanism, for when the chest is expanded it accommodates more blood and allows a greater intake of air, with a small muscular contraction.

The absolute increase in capacity is due to the fact that the content of a cube increases more with the identical increment when the original radius is larger (Fig. 2).

Manwaring in experiments on lungs excised from guinea-pigs showed that the flow of antigen-containing perfusion fluid was promptly arrested by a change in the capillary endothelium. The two following cases show the application of this to human pathology.

A leper at Riverside Hospital was twice transfused. Each time after giving about 600 cc of blood, there was a gradual increasing inspiratory spasm, with expiratory distress. In short there was acute asthma. There was also urticaria. During this attack there was seventh thoracic hyperalgesia. The attack was terminated by the hypodermic administration of adrenalin. Of course, a factor in this case is the sudden increase of blood mass. The respirations of the patient became deeper and the base line was raised on the pneumographic tracing. In the donor's tracing respiration became more and more shallow.

I have had the unfortunate opportunity of examining the lungs in a tragic case of human anaphylaxis which I witnessed. A young sailor, G., was admitted to the Willard Parker Hospital with influenza and developed pneumonia, which may have resulted in increased irritability of his pulmonary vessels. Later he developed

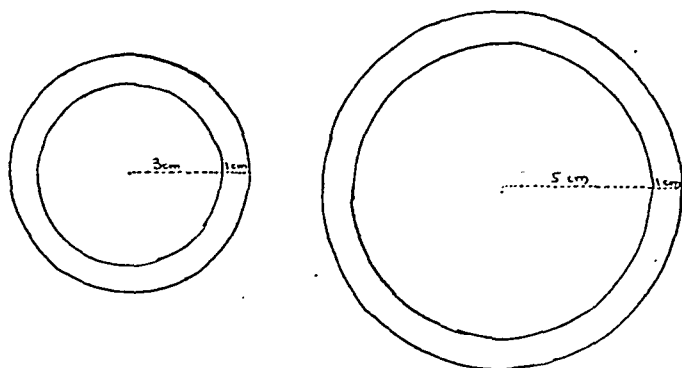


FIG. 2

$$r,^3 \text{ cm.} - r^3 \text{ cm.} = 4^3 \text{ cm.} = 64 \text{ cc} - 27 \text{ cc} = 37 \text{ cc}$$

$$r,^3 - r^3 = 6^3 \text{ cm.} - 5^3 \text{ cm.} = 216 \text{ cc} - 125 \text{ cc} = 91 \text{ cc}$$

With the identical increase of 1 cm. in the radius, the increase of cubic capacity is disproportionately greater, the longer the original radius.

a cerebrospinal meningitis, which was treated with intraspinal injections of serum. Periodic attacks of fever with chills, as well as symptoms of cord pressure and marked emaciation developed. It was thought that there was a walled off focus in the meninges which might be inaccessible to the blood stream. The order to desensitize the patient preliminary to the slow intravenous injection of serum, was disregarded and after 100 cc of diluted serum had been injected within the period of ten minutes the patient suddenly took a deep breath, cried, "My head!", and died with his chest in deep inspiration. An autopsy revealed several walled off meningitic foci. Most interesting was the condition of the lungs, which were emphysematous at the periphery and liver-like from congestion in the center. The right ventricle was markedly dilated.

Michael Grossman of Vienna showed that in animals there was marked diminution of the expansibility of the lung, with diminished

vital capacity, both after the injection of defibrinated blood and after pulmonary congestion induced by muscarin.

It has frequently been observed in the emergency room at Harlem Hospital, that asthmatic patients object to the administration of atropine on the ground that it causes them to be thirsty and the resultant increased fluid intake causes a prompt recurrence of their attacks. Attacks of dyspnea, asthmatic in character, may be induced in some subjects, as nephritics, by the intake of more fluid than can be tolerated. Such attacks often occur after hearty meals.

Injected specimens of an emphysematous (Fig. 3) and a normal lung show the very marked diminution in the arterial bed in the former.

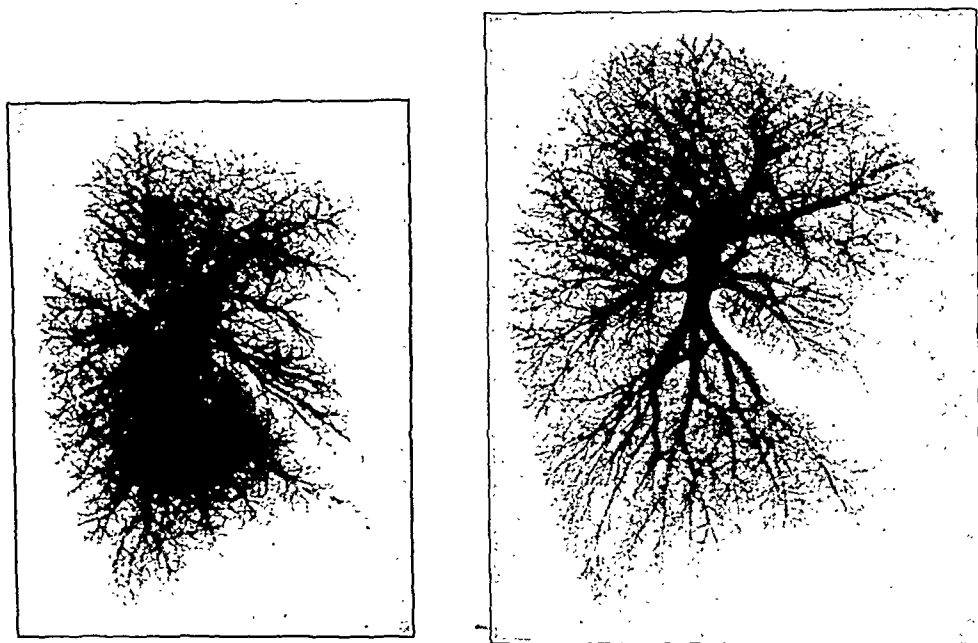


FIG. 3.—Roentgenograms of lungs injected through pulmonary artery with barium gelatine mixture. Left, normal; right, emphysematous. Note increased length and relative narrowing of arteries. (Kindness of Dr. Louis Gross, Montreal.)

It is pertinent to inquire what clinical evidence is offered to support the view that what we have termed the vascular dermatomes and myotomes, correspond to the pulmonary vascular bed, rather than to the distention of the right ventricle or auricle. The distribution of the hyperalgesia and spasm is homolateral to the side of the lesion, as has been observed in pneumonia and in pulmonary abscess. When the hyperalgesia and spasm are bilateral it is more intense and involves more segments on the side of the lesion. Small lesions apparently insufficient to induce general rise in pulmonary pressure may produce a segment reflex. If the reflex came from the pulmonary artery ring it would be referred to the second dorsal segment as in the case of the aorta, because this portion of the



pulmonary artery, like the aorta, arises from the division of the conus arteriosus, the most cephalad portion of the primitive heart. The auricles and ventricles arise from the primitive auricles and ventricles and are represented on the chest by the fourth and sixth thoracic segments. The ventricular reference was manifest in a case of lung abscess to be mentioned.

The primitive sinus venosus which has a low-lying segment representation, is included in the right auricle and would be unaffected by pulmonary congestion. The ducts of Cuvier, originally below the diaphragm, enter the sinus venosus. Organs arising caudad to these veins remain subdiaphragmatic and their segmental representation is the eighth thoracic and below, though the veins themselves enter the chest.

A patient with a lung abscess in the right lower lobe, subsequent to an ambulatory pneumonia, showed hyperalgesia limited to the typical visceral and vascular areas, excepting during attacks of increased toxemia, with physical signs of impaired heart action. At such times he showed in addition, fourth thoracic segment hyperalgesia.

The view that the cephalad segments represent the visceral distention is clinically supported by the following observations:

Several children old enough to give intelligent answers, in whom there was a diphtheritic membrane, involving the larynx, trachea or bronchi, were observed. In these patients there is at first very little inflammatory reaction, which diminishes promptly after the administration of antitoxin. In them a pure visceral distribution of the hyperalgesia occurred and an increase in the tonus of the muscles innervated by the cephalad group of segments was maintained.

Recently at the Harlem Hospital I had the opportunity of observing an undernourished woman who entered with the diagnosis of pneumonia and who had classical physical signs. There was a marked increase in the tonus of the muscles of the upper part of the chest. The morning following the expectoration of membranous casts from her trachea and bronchi, she did not show any hyperalgesia of the seventh thoracic segments. There was marked hyperalgesia of the cervical group of segments. A culture from her trachea showed diphtheroid organisms and pneumococci. Thickening of the trachea and bronchi was visible in the roentgenograph.

Another group of patients are those in whom the vascular areas disappear by reason of the diminution of the blood mass. A patient with abscess of the lung had a left lower lobe pneumonia, Type I, for which he received serum. During this time he showed marked visceral and vascular hyperalgesia, with tonic fixation of the chest in partial inspiration. Subsequently he developed a typical abscess of the lung with classical physical signs and radiographic findings. A number of times the abscess emptied itself spontaneously; after

each emptying the hyperalgesia and pain in the neck, previously severe, disappeared. A vascular zone was absent during this entire period. This man had lost, by reason of his septic sweats, upward of 40 pounds. Finally he was examined bronchoscopically and pneumococcus serum was injected into the cavity. The patient then recovered and when last seen there was no hyperalgesia whatsoever and he had regained his former weight.

It is proper to inquire what can be learned by a study of the visceral and vascular groups of pulmonary reflexes. In upward of 100 patients suffering from pneumonia, the hyperalgesia and muscle spasm was most marked and extensive on the side homolateral with the lesion. It was impossible from a study of the reflexes, to determine what lobe of the lung was involved. The extent of the lesion did not correspond with the intensity or the extent of distribution of the hyperalgesic zones. This seems rather to be an expression of the amount of irritation and of the irritability of the nervous system. A very small lesion may show a very marked or extensive hyperalgesia and spasm. A very extensive one may show very slight hyperalgesia and very slight increase of muscle tonus.

A colored longshoreman had a typical lobar pneumonia with very slight hyperalgesia and practically no limitation of the respiratory excursion. He came to the Hospital because he felt dizzy rather than because of any respiratory symptom.

In advanced pulmonary tuberculosis the vascular segments are usually not irritated because of the emaciation, and consequent relative diminution of pulmonary congestion.

With the disappearance of the irritating lesion, the hyperalgesia and muscle spasm disappear. They disappear before the lesion, only when the nervous system is overwhelmed. A boy, aged seventeen years, had pneumonia last spring. The hyperalgesia and muscle spasm have not disappeared though other gross physical signs are absent. The fluoroscope, however, still indicates the location of the lesion.

A woman, aged sixty-six years, had a pneumonia five years ago with marked hyperalgesia, which persisted for months. At present there are neither hyperalgesia nor other physical signs.

Frequently at Harlem Hospital we have been able to note in pneumonia patients the disappearance of the physical signs synchronously with the disappearance of the hyperalgesia.

**Summary.** The pulmonary bud springs from the anterior esophageal wall and grows into the post-bronchial plexus; a separate visceral and vascular segment representation results and is of semeiological importance.

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## CARDIODYNAMICS OF ARTERIAL HYPERTENSION.

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ONE thing common to the entire group of individuals with persistent elevation of blood-pressure consists of certain mechanico-pathological changes in the heart and arteries. These alterations do not vary with the individual case except in degree, and it is largely their effects upon the comfort and welfare of the patient that characterize the clinical course of arterial hypertension. The accuracy of our understanding of circulatory dynamics determines in large measure the correctness of our efforts at therapeutic control and of the conclusions we ultimately arrive at as to prognosis.

The general biological law of action and reaction within the body is strikingly illustrated in hemodynamics. The problem of circulating the blood appears to be, so far as the heart is concerned, a purely mechanical one. It has to negotiate by force the sum of the resistances—passive and active—opposed in and by the vascular channels so as to overcome the inertia of the contained blood mass. It is obvious that the heart could not long successfully function as a mechanism without the interposition of resistance in the circulation to take up and utilize its energy. With certain minor reservations, resistance in the vascular circuit and blood-pressure may be considered as the same thing, and practically all physiological variations in arterial and capillary pressures are to be looked upon as constituting the normal mechanism for securing the proper distribution of blood to the various organs and tissues of the body. The constantly varying needs of the body are met by equally varying adjustments in the circulation which are effected by vasomotor control. Vasomotor tonus, as it is manifested in the capillary and precapillary beds, is the agency whereby resistance is thrown into the circuit, regulating thereby the degree of inertia which the heart has to overcome to maintain an effective circulation. Without this interplay of

resistance and force, life and normal physical activities could not go on. In conditions of shock and collapse, the relaxed and toneless bloodvessels reduce resistance to so low a point that the unopposed heart pump is unable to beat up a blood-pressure sufficient to meet physiological requirements.

This opposition, as between vascular circuit and heart demanded by a normal physiology, becomes, in certain conditions and as a result of certain imperfectly understood factors, greatly exaggerated, and we have in consequence a circulatory vicious circle which, if not relieved, becomes in time a source of the greatest peril to the entire mechanism. In this state, which we designate "arterial hypertension," the heart and arteries appear to be in conflict. As the vascular resistance rises, the heart power increases and so the contest rages under some morbid stimulation until one or the other is victor—either the valiant heart becomes exhausted or a breach is made in the circuit.

The velocity and tension (pressure) in the arterial system are dependent upon the energy (power) of the heart and the resistance in the peripheral vascular channels. If the energy of the heart increases, the peripheral resistance remaining constant, both tension and velocity become greater. Should, however, resistance increase at the same time as the heart's energy, the tension will rise in the arterial system and velocity of blood flow vary according as the peripheral or cardiac factor is in excess. This is the reciprocal interplay so long as certain bounds are not passed and the heart muscle is competent.

There is comparatively small reservoir capacity in the arteries. Such as there is depends upon the elastic stretch of the arterial walls. Their maximum extensibility lies slightly above the usual systolic pressure in health (Schäfer). At that point the arteries are able to receive a relatively large amount of blood from the heart without undue increase of tension. Above that limit the cubic enlargement of the arteries is less and less with each fresh increment from the ventricle until they become rigid and taut, or, yielding to pressure, undergo dilatation. The arteries now having received their maximum load, further increase must be taken care of either by back pressure upon the heart or by increased escape through the capillary network. Very high pressure in this way tends to increase the amount of residual blood in the ventricle and thereby to place the heart pump at a disadvantage. In health this effect is prevented by automatic stimulation of the cardiac depressor nerve, thus slowing the heart, and by lowering of vascular tonus through the intervention of centers in the medulla. Thus, the strain is eased up and conditions gradually become readjusted. In certain pathological states characterized by continuous high blood-pressure, this regulatory mechanism is insufficient to meet the needs of the situation, and pressure remaining

high, the heart must take up the burden. Furthermore, in persistent hypertension, it is likely that the factor of stretch or elasticity of the great arterial trunks, which normally aids in taking up increments of pressure, soon becomes seriously impaired so that hypertension of any duration is possible only by virtue of compensatory cardiac hypertrophy. The heart muscle fortunately possesses the capacity to grow, within limits, in proportion to the work demanded of it. This is the law of compensatory hypertrophy common to all hollow muscular viscera. This protective endowment implying when operative, an adequate cardiac reserve, is always salutary so far as the circulation is concerned, and only when this reserve becomes exhausted will circulatory failure supervene. Cardiac potential may suffice for long periods with little appreciable embarrassment, but in general in the course of time with persistence of overstrain it becomes exhausted. Up to this point, hypertrophy has saved the situation. Dilatation now will render the ventricle unable to empty itself sufficiently, and the blood will tend to accumulate within its cavity. The left auricle will now have to take up the circulatory slack with slowing in the pulmonary circuit, right heart insufficiency and general venous stasis following in sequence. Aside from fatigue of and molecular degenerative changes in the heart fiber, persistent hypertension appears to be a direct excitant of changes in the arterial walls, so that in time the arteries become tortuous and relaxed, constituting what Norris has called a break in vascular compensation. This fibrous sclerosis of the arteries, by causing them to lose much of their elasticity, may necessitate as a consequence a greater blood volume in order to supply the organs and tissues with their proper quota. This throws still greater strain upon the heart, adding to the already heavy burdens of that organ.

The hypertrophied heart of high blood-pressure is then a powerfully acting organ, valiantly striving to overcome the obstacles which interpose in the path of the blood stream. However adequately it may appear to meet this demand upon its powers, it is nevertheless foredoomed to failure, for its very increase in size and energy implies inroads on its reserve, and, moreover, it seems unlikely that the coronary circulation increases in adequate ratio to its augmented nutritive needs. To designate the sthenic powerful heart of high blood-pressure as a degenerated or sclerotic organ, or as being the seat of "chronic myocarditis," as is often done, is, however, to misunderstand the vital mechanism at work. It is more potentially than actually diseased and what pathology may later develop in the stage of exhaustion represents the accumulated effects of fatigue and nutritive ischemia.

During the stage of adequate cardiac compensation, the circulation, to all appearances, is carried on normally. In the main, the elevated blood-pressure may be considered as evidence of

relatively normal heart power and normal blood flow. Yet, we must not assume that volume blood flow runs proportional to blood-pressure, inasmuch as the factor of peripheral resistance must be taken into account. Neither is it correct to infer that an abnormally high blood-pressure constitutes an indication of normal cardiac power, for, as Norris rightly emphasizes, the last ounce of reserve power of the heart may be put forth in maintaining this very pressure and the heart muscle be at the point of failure notwithstanding a pressure above normal. In the end, the arterial pressure must drop when ventricular failure supervenes. Decline in pressure from dilatation affects mainly the systolic end of the blood-pressure formula, diastolic pressure showing less decrease, or even in certain cases becoming somewhat augmented. In either case there results a reduction in pulse-pressure, signifying loss of driving power from the heart and slowing down of the mass movement of the blood. The fall in systolic pressure is rarely abrupt—perhaps only in the occasional instance of acute cardiac dilatation following severe overstrain or infection, or when terminal collapse occurs when a further sudden antemortem decline ushers in the end. Even with the signs of failing circulation—edema, visceral stasis, serous dropsy—present throughout the body, the blood-pressure may still remain considerably above the normal. Indeed, it may be said that there are no definite rules whereby we are altogether safe in judging the import of either a rise or fall of blood-pressure. In patients seriously embarrassed, a rise of blood-pressure may denote a restoration of compensation and general improvement, whereas in certain other cases it may be unfavorable, implying the advent of uremia. On the other hand, a fall in pressure may be a favorable indication, signifying a lessened toxemia and diminished peripheral constriction. High blood-pressure is consequently not necessarily an index of good circulation, nor is a lowering pressure a sign of poor circulation. The claim that arterial hypertension is a conservative mechanism rendered necessary to maintain an effective working of the organs, especially of the kidneys, does not receive striking confirmation from clinical experience, for many patients appear to profit greatly and suffer no decline in elimination when a high blood-pressure is lowered by effective treatment. To place implicit trust in instrumental readings as an index of progress or prognosis in any given case is to invite error and misunderstanding. The patient's general condition and comfort, his range of efficiency, the presence or absence of well-attested signs of circulatory embarrassment constitute a better basis for prognosis than any information procurable from blood-pressure readings alone.

Heart failure in arterial hypertension is encountered in one of three forms: It may supervene suddenly, either as an acute

dilatation following upon severe sudden physical overstrain, or during an infection, or the heart may stop abruptly during an angina. It is probable that sudden heart arrest is always associated with serious coronary disease. By all means, the most frequent clinical development of cardiac failure is a gradual one with progressive decline in blood-pressure, venous stasis, secondary renal insufficiency and death from asystole. The period covered by these developments may stretch over many weeks or months, there being a certain susceptibility to treatment so long as the heart muscle is capable of responding to stimulation. Less frequent than this form of chronic failure, but still far from rare, is circulatory failure by arterial stasis—so-called “high blood-pressure stasis.” In this type of cardiac exhaustion, peripheral constriction is predominant and the mass movement of the blood rendered difficult by the inability of the heart to force the capillary narrows. The systolic pressure is often maintained, although pulse-pressure suffers from elevation of diastolic pressure. The heart beats rapidly with full force, striving with its last ounce of energy to secure peripheral outflow, but without success, finally succumbing through exhaustion.

During the sthenic stage of arterial hypertension, while cardiac compensation is maintained, the pulse is moderate or slow and usually regular in rhythm. Premature contractions may occasionally alter its beat. The electrocardiogram displays ordinarily a normal mechanism often with left ventricular preponderance. Such conduction anomalies as may appear in individual cases are not sufficiently common to possess especial significance. Auricular fibrillation is notably uncommon in the high-pressure heart. When it does occur it need not necessarily constitute an immediate source of danger, although it unquestionably imposes an additional handicap on an already embarrassed heart. Experience shows that the heart can for even long periods forego the assistance of auricular systole and maintain an efficient circulation, although perhaps at a somewhat lower functional level. A perversion of normal heart rhythm, known as “gallop rhythm,” is encountered with considerable constancy when high-pressure stasis has developed. On listening to the heart, a third sound is heard in late diastole, changing the rhythmic sequence of sounds from two-four to three-four time, imitative of a horse’s gallop. The cause of this third sound is still in doubt, but it is supposed to be produced by forceful auricular systole. Gallop rhythm possesses grave prognostic significance. It is usually associated with alternating pulse, which has a similar although less immediate unfavorable import. In the presence of both gallop rhythm and alternating pulse, the heart-rate is persistently rapid. Continuously rapid pulse in high blood-pressure conditions is an unfavorable event, signifying, as a rule, the approach of cardiac breakdown.

Attempts have been made to interpret certain factors in blood-pressure readings as indicative of heart load and volume output and therefrom to deduce, by mathematical computation, degrees of cardiac strain and efficiency in terms of prognosis. If this could be done with reasonable exactness, it might prove a valuable aid in observing the progress of a case. The pulse-pressure has been regarded, with certain qualifications, as an index of the cardiac output per beat. This appears to be a plain and obvious inference if our interpretation of the blood-pressure formula be correct. A high pulse-pressure signifying a greater heart load—increased output per beat—might reasonably be interpreted as a factor making for exhaustion of reserve and earlier failure of potential. As a matter of fact, clinical experience does not strikingly confirm this assumption, a high pulse-pressure being successfully negotiated for long periods by many hearts, so that the rule cannot be applied. The claim is also made that heart-rate times pulse-pressure establishes mathematically the output per minute—in other words, the blood flow from the heart. It is difficult to decide how exact a criterion this may prove. It certainly is not true for aortic regurgitation and certain cases of aortic atheroma, and it probably should not be trusted implicitly or be adopted as a rule.

The existence of patients with persistent high blood-pressure is beset with many hazards. Chief among these are cerebral apoplexy, kidney insufficiency, angina pectoris and heart failure. Should the patient successfully run the gamut of these perils and escape death from intercurrent infections and the degenerations, he will eventually become actually what he has always been potentially—a cardiac invalid. By the time myocardial exhaustion becomes apparent, the prolonged effects of vascular overstrain have so undermined the integrity of the arteries as to deprive them of a large part of their capacity to assist the heart in helping on the circulation of the blood. This elastic contractile coöperation from the arteries so necessary to the circulation during the heart's diastole can never be restored, so that the heart must bear an unfair burden in maintaining mass movement in the circulation. Furthermore, although in other forms of cardiopathy, the therapeutic influence of rest may be brought to bear effectively to restore the heart's reserve, success in this direction is never more than relative in arterial hypertension. No matter how completely physical rest may be enforced, blood-pressure is never reduced to normal thereby. The element of cardiac overstrain from high peripheral resistance still persists and continuously operates to the detriment of the heart fiber. This is not to imply that therapeutic control by rest and other measures of treatment is ineffectual, but rather that we cannot expect, because of mechanical conditions present, the same degree of restoration of function as is possible in certain other forms of heart failure. Once cardiac



insufficiency has frankly made its appearance in arterial hypertension the course of events is steadily downward, although the end may be long postponed. This emphasizes the importance of recognizing the earliest signs of circulatory failure. Ordinarily, this is not difficult to the attentive observer. Other things being equal a change from the deliberate, slow and measured heart-rate ordinarily present in high blood-pressure to one persistently more rapid than normal signifies the advent of myocardial insufficiency. It is a fair assumption that this rapid rhythm is an effort on the part of the ventricle to compensate by increase of stroke for reduced volume output. Progressive elevation of diastolic pressure is to be watched with the greatest concern, and when observed the urine and blood nitrogen derivatives should be carefully studied. Decline of systolic pressure, if not attributable to therapeutic measures and if associated with increasing subjective discomfort, possesses unfavorable significance. Edema, alternating pulse, gallop rhythm, nocturnal asthma, Cheyne-Stokes breathing need no emphasis as to their implication.

The aim of treatment in this, as in other forms of heart failure, must be to conserve the resources of the heart so as to maintain an efficient circulation for as long as possible. In treating this condition, which may and usually does last for years, extremes should be avoided. We should endeavor to accomplish our purpose with the minimum restriction of and interference with the general activities of the body. Much instruction of the patient will be necessary to secure his coöperation in carrying out a policy of heart conservation. Success or failure hinges largely upon the willingness of the patient to accept restrictions, but often failure is invited by our own mistakes, through imposing a hygiene which is too rigorous. Tact and understanding combined with firmness are necessary, for the patient must make friends with his malady and learn to live on good terms with it.

The suggestion has recently been made by Norris that hypertensive cardiovascular invalids be sent to sanatoria or other suitably adapted institutions where, during periods sufficiently long to ensure results, they be instructed in a new personal hygiene suited to their altered circulatory state. Such a plan might be most profitably followed with patients able to command the time and means necessary, but their number must, of necessity, prove but a small percentage of individuals afflicted with high blood-pressure. With most patients, instruction must come from their personal physician.

Time will not permit of our discussing in detail the methods of treatment available for the control of high blood-pressure. During the period of adequate cardiac compensation such measures as are advised should be as accurately as possible adjusted to the temperament, economic necessities and environment of the patient,

but should always include as a prominent consideration the conservation of heart power, for it is upon that factor that the eventual welfare of the patient depends. What may be accomplished in this direction can only be brought about by a thorough understanding and coöperation between patient and physician, and such a relationship is achieved only by instruction of the patient in the full detail of personal hygiene. We should in this matter seek to duplicate the practice followed in the modern treatment of diabetes and tuberculosis. Concentration of attention on the instrumental record of the blood-pressure will prove a great mistake. The criteria of a good or a poor circulation do not rest in degrees of pressure or millimeters of mercury of the sphygmomanometer.

With the advent of the asthenic stage, or period of cardiac insufficiency, active therapeutic control becomes necessary. As soon as it is apparent that the heart is yielding to the overload, physical rest should be enforced. In no other manner may cardiac reserve be restored. During physical relaxation, pressure declines somewhat and cardiac adequacy improves. Combined with rest, more careful control of diet and freer elimination become advisable. The state of renal function, which should be determined by the methods of blood chemistry and kidney function testing, enters here as an important consideration. After rest has been sufficiently enforced, resumption of activity should be gradual and under strict supervision. If there exist serious indications of high pressure stasis, considerable benefit may be secured from venesection, provided no contraindication, such as anemia, uremia or dropsy, exists. The reduction of pressure, especially diastolic pressure resulting from a free abstraction of blood may last for several days and may ease the ventricle sufficiently to avert the threatened stasis. There is something to be said for the employment of venesection as a gradual remedial measure repeatedly carried out to a moderate depletion at appropriate intervals in plethoric patients displaying tendency to pressure stasis. Care must be exercised not to extract too much blood nor to repeat the measure at too frequent intervals, otherwise harmful depletion of the blood plasma may result. It is better not to attempt venesection at all in nephritis with nitrogen retention.

Our last stand in failing heart of hypertension is digitalis. It does little good in high-pressure stasis, especially when renal inadequacy exists and uremic bodies are accumulating rapidly. It may be tried even in these cases, but not with great hope of success. In ordinary gradual ventricular failure with progressively falling systolic pressure, venous stasis and edema, its action is more encouraging. The method of employing digitalis in this type of case should be more conservative than in auricular fibrillation, for it is not vagus stimulation and slowing of the heart we are

after so much as its effect upon myocardial tonus. Thorough digitalization is not indicated and had better not be attempted. The tonic method of digitalis medication, long ago advocated by Balfour, should be the one chosen and, having determined the optimum dosage, this should be continued as long as response is secured. The failing heart of high blood-pressure working ever upon the verge of breakdown cannot be trusted to take care of itself without support.

## CONGENITAL MALFORMATIONS OF THE AORTIC AND PULMONARY VALVES.

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CONGENITAL malformations of the aortic and pulmonary valves of the heart are not common findings at postmortem examination. The malformations found here are either an increase or a decrease in the number of cusps forming the valves. In approximately 2000 postmortem examinations I have encountered 2 instances, 1 in the aortic and 1 in the pulmonary valve. The frequency of malformations of these valves is shown in Table I:

TABLE I. RELATIVE FREQUENCY OF MALFORMATIONS OF THE AORTIC AND PULMONARY VALVES FOUND AT NECROPSY.

	Number necropsies.	Aortic valve.		Pulmonary valve.	
		2 cusps.	4 cusps.	2 cusps.	4 cusps.
Simpson <sup>1</sup> . . . .	4,252	5	0	1	4
de Vries <sup>2</sup> . . . .	3,600	12	1	3	9
Thilo <sup>3</sup> . . . . .	5,814	1	1	2	2
Simonds . . . . .	2,000	1	0	0	1
	<hr/>	<hr/>	<hr/>	<hr/>	<hr/>
	15,666	19	2	6	16
Babes <sup>4</sup> . . . . .	10,000	7		4	
	<hr/>	<hr/>		<hr/>	
	25,666	26		10	

In Babes's series of 10,000 postmortem examinations he mentions only instances of two cusps in the aortic and pulmonary valves. From Table I it appears that the most common type of malformation of these valves consists of two cusps in the aortic and four cusps in the pulmonary valve, each occurring in the proportion of about 1 in 1000 necropsies. Two cusps in the pulmonary valve are encountered

<sup>1</sup> Jour. Anat. and Physiol., 1899, 32, (N.S. 12), 679.

<sup>2</sup> Beitr. z. path. Anat., 1918, 64, 39.

<sup>3</sup> Zur Kenntnis der Missbildungen des Herzens, Diss., Leipzig, 1909.

<sup>4</sup> Arch. f. path. Anat., 1891, 121, 562.

about once in 2500 postmortem examinations; and four cusps in the aortic about once in 8000 autopsies. De Vries in Amsterdam found the highest percentage of these malformations; namely two cusps in the aortic valve once in 300 autopsies; four cusps in the pulmonary valve once in 400; two cusps in the pulmonary once in 1200; and four cusps in the aortic valve once in 3600.

An analysis of more than 200 cases of malformation of these valves collected from the literature gives a somewhat different impression as to the relative frequency of the several types of anomaly. These cases are tabulated in Table II.

TABLE II. GROUPING OF CASES COLLECTED FROM THE LITERATURE OF MALFORMATIONS OF THE AORTIC AND PULMONARY VALVES.

Lesions.	Number of cases.
Aortic valve:	
2 cusps . . . . .	58
4 cusps . . . . .	5
5 cusps . . . . .	1
Pulmonary valve:	
2 cusps . . . . .	88
4 cusps . . . . .	48
5 cusps . . . . .	2
Aortic and pulmonary valves:	
2 cusps in each . . . . .	4
	<hr/>
	206
2 cusps in aortic valve with pulmonary valve as a diaphragm with small opening . . . . .	1
3 cusps (one being small and rudimentary) in each vessel . . . . .	1
Aorta and pulmonary not separated, common trunk with 4 cusps . . . . .	1
	<hr/>
	209

It would appear from the above Table II that two cusps in the pulmonary valve is the most common of these malformations. This is due to the fact that this anomaly is so frequently associated with other more serious congenital malformations of the heart that a much larger number of such cases have been reported. Many of the cases included in Table II were reported on account of the more serious malformation, the anomaly of the pulmonary valve being mentioned only incidentally. As will be pointed out later, however, there is probably a very definite relation between the presence of two cusps in the pulmonary valve and the other malformations present in the heart.

The two instances of malformation of the aortic and pulmonary valves which I have encountered occurred in cases of sudden death in which no clinical history was obtainable. There was no evidence, however, in either case that the anomaly had anything to do with the death of the patient or that they gave rise to any murmurs that could have been detected on physical examination. These cases are as follows:

CASE I. *Four Cusps in the Pulmonary Valve.* This patient was a white male, aged fifty-seven years, who collapsed suddenly while at lunch and died in about five minutes. At postmortem examination the heart was found to be hypertrophied, this being limited to the left ventricle. There were a number of grayish-white scars in the pericardium which extended for distances of 5 mm. into the substance of the heart muscle. The tricuspid valve was smooth and thin. The mitral and aortic valves showed a moderate degree of yellowish-white thickening. Both coronary arteries were markedly sclerotic and calcified. The myocardium showed numerous grayish-white streaks and masses of fibrous tissue, especially in the wall of the left ventricle. In the aorta there were marked atheromatous changes with extensive calcification. The lungs, stomach,

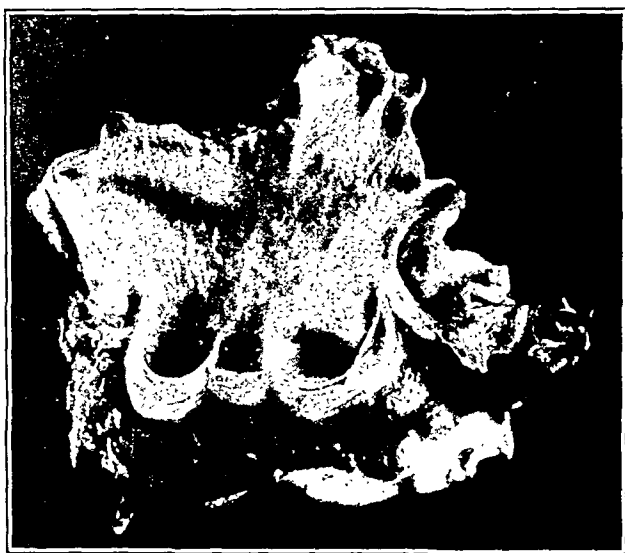


FIG. 1.—Four semilunar valves in the pulmonary artery. One of the two larger cusps has been cut in two in opening the vessel.

intestines, liver, spleen and brain showed no important gross changes. The kidneys were somewhat larger than normal and red in color; the capsule stripped fairly easily leaving a slightly granular surface; the cortex measured 5 to 7 mm. in thickness and the cortical markings were distinct; in the right kidney were a number of retention cysts of small size.

The pulmonary valve of the heart was composed of four cusps. Two of these measured 2 cm. along their free edges. The other two cusps together measured 2 cm. along their free borders; the smaller of the two was completely formed except for the lack of a corpus Arantii and measured 8 mm. along its free edge and 6 mm. in depth, and showed a fenestra near its free margin measuring 2 mm. in diameter. The larger of these two cusps was also completely

formed except for a corpus Arantii and measured 14 mm. along its free edge and 100 mm. in depth. The two larger cusps showed corpora Arantii. All of the cusps of this valve were smooth, thin and translucent.

CASE II. *Two Cusps in the Aortic Valve.* This patient was a white male, apparently about fifty years of age, who was found dead. At postmortem examination his heart was not noticeably hypertrophied; the right heart chambers were enormously distended with dark clotted blood. There were numerous punctate hemorrhages in the pericardium. The tricuspid and pulmonary valves were normal in



FIG. 2.—Two semilunar valves in the aorta. The line of incision in opening the vessel did not pass exactly between the cusps and a small part of the anterior valve can be seen along the right edge of the specimen. The origin of the left coronary artery as two vessels is visible; the opening of the right coronary artery is hidden by the end of the cusp to the left. The ridge on the aortic wall behind the anterior cusp is just visible. The aneurysmal dilatation of the posterior sinus of Valsalva can also be seen.

appearance. The mitral valve showed areas of yellowish thickening, but its shape was not distorted and it appeared to be competent. The coronary arteries showed a moderate degree of arteriosclerosis. In the myocardium there were numerous streaks of white fibrous tissue. The lungs crepitated throughout; from the surfaces made by sectioning large quantities of frothy fluid escaped on pressure. The stomach, liver and spleen showed no gross changes. The kidneys were slightly enlarged; their capsules stripped with some slight difficulty, leaving a faintly granular surface; the cortex measured 5 to 7 mm. in thickness and the cortical markings were not normally distinct. The brain was moderately edematous but otherwise showed no gross changes.

The aortic valve consisted of two cusps, an anterior and a posterior, both moderately thickened especially along their free borders. These cusps were approximately equal in size, measuring 32 and 31 mm. respectively along their free edges. Both coronary arteries were given off from the anterior sinus of Valsalva. The left coronary occurs as two vessels, 2 mm. apart, one being approximately twice the size of the other. The larger of these two vessels arises at a place in the aortic wall 2 mm. from the point of junction of the two cusps and on a level with the upper margin of the valve. The left coronary artery arises at a place about 2 mm. from the junction of the opposite end of the cusp with the wall of the aorta, and approximately 2 mm. below the level of the upper margin of the valve. At a place nearly opposite the middle of this cusp there is a low ridge on the aortic wall averaging 1 mm. in width, and extending downward in the sinus of Valsalva to the attached margin of the valve but not extending on to the cusp itself. The two cusps are adherent along their adjacent borders on the right for a distance of 2 mm. Each cusp has a corpus Arantii. In the posterior sinus of Valsalva the aortic wall bulges backward producing small aneurysm-like pockets. There are small patches of yellowish thickening in the wall of the aorta in the sinuses of Valsalva, but the lining of the ascending portion of the arch is smooth. The circumference of the aorta at the level of the upper margin of the valves measured 6.5 cm.

The presence of four cusps in the pulmonary valve of Case I without any evidence of any present or previous inflammatory process renders it extremely probable that this is a definitely embryonic malformation and not one which owes its origin to an endocarditis which resulted in the formation of a synechia between one of the cusps and the wall of the pulmonary artery. The mode of origin of this anomaly is not readily determined. The following possibilities may be considered:

1. In the development of common vascular trunk which later becomes separated into the aorta and pulmonary artery, there appear four distal and two proximal pads of tissue or swellings on the inner surface of the vessel.<sup>a</sup> The distal swellings form the semilunar valves of the two vessels by the descent, in a clockwise spiral direction, of the partition which separates the common trunk into two vessels. This partition splits the right and left distal swellings or pads in such a manner that the aortic valve is composed of the original posterior and one-half of each of the right and left swellings, while the semilunar valves of the pulmonary artery are formed from the original anterior and the anterior halves of the right and left swellings (Fig. 3). If, as a result of maldevelopment, a fifth swelling is intercalated between the anterior and one of the lateral swellings, a fourth cusp will appear in the pulmonary artery when the process of separation is complete (Fig. 4).

2. After the descent of the septum which divides the common

trunk vessel into aorta and pulmonary artery, the swellings become hollowed out from above to form the cusps of the semilunar valves. This hollowing-out process may not occur in the normal manner in one of the pads, but in such a way that there is left a partition dividing one of the cusps into two.

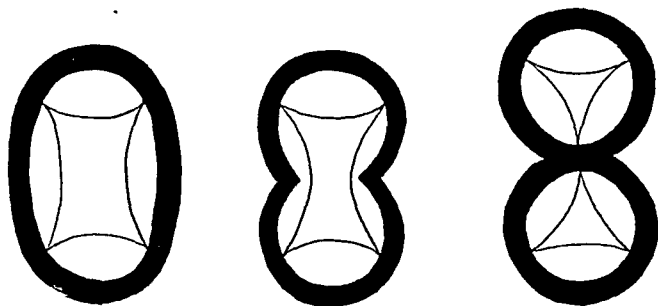


FIG. 3.—Diagram showing the normal development of the aorta (upper) and pulmonary artery (lower) from the common vascular trunk.

3. If the dividing partition is shifted from its normal position and descends in such a manner that it divides the right lateral swelling at the normal place, namely its center, but the other side of the partition is shifted too far backward and divides the posterior swelling near its left border, this would leave parts of all four swellings in the pulmonary artery and thus form four cusps to its valve. This method of malformation would necessarily cause an associated reduction in the number of aortic cusps to two. Inasmuch as no case of four cusps in the pulmonary artery and two in the aorta appears to have been reported in the literature it would seem very

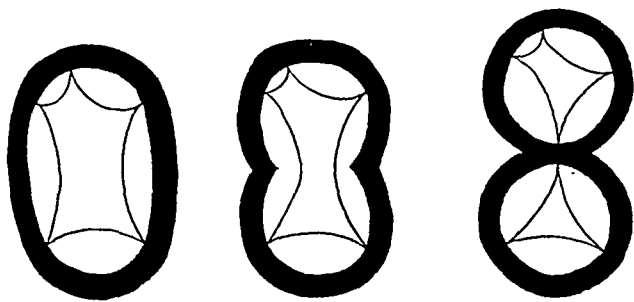


FIG. 4.—Diagram illustrating a possible mechanism for the development of four cusps in the pulmonary artery by the interpolation of an extra swelling or pad in the common vascular trunk.

unlikely that four cusps in the pulmonary valve originate in this way. The same applies to the corresponding anomaly of the aortic valve.

It is not always possible to determine with precision in any given case whether the presence of four cusps in the pulmonary valve resulted from the presence of an extra intercalated distal swelling in the



common vascular trunk, or from an abnormal process of hollowing out of one of the normal swellings. It would seem to be a logical assumption that if the supernumerary cusp were due to an improper process of hollowing out of a normal swelling, there would be more or less fusion of the adjacent edges of the two cusps thus formed; there would be the appearance of one large or normal-sized cusp with a partition. If the anomaly were due to the presence of an extra swelling the common trunk, the cusp formed from it would be distinctly and definitely separate. Inasmuch as the extra cusp in Case I (Fig. 1) is so distinct and shows no evidence of fusion with either of its adjacent fellows it appears probable that in this case the malformation resulted from the presence of an intercalated swelling in the common vascular trunk. The same possibilities apply to the presence of four cusps in the aortic valve.

In those instances in which four semilunar valves are present in the aortic or pulmonary ostium the cusps appear to be perfectly adapted to each other, so that the valve as a whole is competent.

In cases of reduction of the number of cusps in the aortic and pulmonary valves, the two cusps may be approximately equal in size, as in Case II (Fig. 2), or one may be considerably larger than the other. Furthermore, in the case of the aorta, the coronary arteries may come off from the same sinus of Valsalva, as in Case II, or each sinus may give origin to a coronary artery. The mechanism by which this anomaly is produced probably varies in different cases. The following possible mechanisms are suggested:

1. Fusion of two of the cusps as a result of some inflammatory process, either prenatal or postnatal. In the latter instance, of course, the condition could not be considered as a congenital malformation. Two adjacent cusps may fuse and the partition formed between them be later ulcerated away, by an endocarditis or be absorbed in some other way, leaving a single sinus of Valsalva. The probability of fusion with subsequent disappearance of the partition is strengthened by the presence in the wall of the sinus behind one of the cusps of a ridge which may or may not extend on to the valve itself. In Case II, there is such a ridge. The significance of a ridge of this kind is not always clear. If fusion of the two cusps occurs after the two valves are fully formed it would appear likely that the single cusp thus produced would be larger than its fellow. It may be objected to this statement that the process of adaptation of the cusps to the aortic or pulmonary opening may result in more or less equalizing of their size. It appears probable, however, that the process of equalization would be more readily accomplished if the fusion occurred before the solid pads of tissue had been hollowed out to form the semilunar valves. This leads to the second possibility in the production of this anomaly.

2. Fusion of the two halves of the lateral swellings at the time of the descent of the septum which separates the aorta from the pul-

monary artery. The partition which separates the two large vessels pushes inward from the right and left cutting the right and left swellings. When the descending ridge advances from the two sides carrying with it the halves of the right and left pads, these halves may fuse in one or the other or in both of the two vessels thus formed; in this way, one vessel, or even both, would have but two cusps which would later be hollowed out to form two cusps instead of the usual three. It seems possible that two cusps of approximately equal size would be produced more readily in this manner than by the fusion of two completely differentiated and hollowed-out cusps. The resulting abnormal cusp might readily show a ridge on the aortic (or pulmonary) wall in the sinus of Valsalva.

3. Shifting of the descending partition to an abnormal position in the common trunk. If the descending partition is so located that on one side it cuts the lateral swelling at the normal place at its center, and the other side of the partition is placed either too far for-

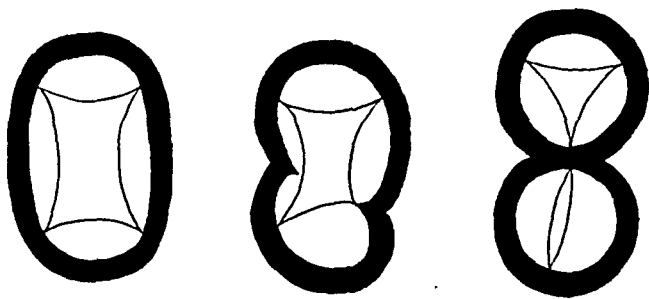


FIG. 5.—Diagram showing possible mechanism for the formation of two semilunar valves in the aorta as a result of deviation of the septum which separates the common trunk into aorta and pulmonary artery.

ward or too far posteriorly and descends between the other lateral swelling and either the anterior or posterior pad, the result would be two cusps in one vessel and three in the other (Fig. 5). The location of the anomaly would depend on the direction of the shifting of the partition. If the reduction of the number of cusps originates in this way, it is evident that one of the cusps in the reduced aortic valve must always be formed from the posterior pad, while one of those in a reduced pulmonary valve will always come from the anterior swelling. The second cusp in such a reduced valve, whether aortic or pulmonic, would be formed from one-half of either the right or left pad, depending upon the direction of the abnormally descending partition. And one of the cusps of the other valve, that is, the one with the normal three cusps, would be formed from the whole of the right or left pad as the case may be. That this is the mechanism by which the reduction takes place in some instances is indicated by the fact that in many cases there is a narrowing of the vessel with two cusps and a widening of the one with three.

The probability of the reduction in the number of pulmonary valves being due to an abnormal shifting of the partition which separates the common trunk into two vessels is further strengthened by the greater frequency with which this anomaly in the pulmonary artery is accompanied by other more serious malformations of other parts of the heart. This will be discussed later.

4. The presence of three distal swellings in the common trunk instead of the normal four. If the anterior or posterior distal swelling is lacking in the common trunk the corresponding vessel will have only two semilunar valves.

In a given case of reduction in the number of the aortic valves it is not often possible to determine which of the above mechanisms was responsible. The direction of the opening between the two cusps does not furnish reliable information on this point. For it would seem that the adaptation of the two cusps to their function of closing the ostium would of necessity result in some shifting of the direction of the opening from its original direction. The location of the coronary arteries also does not give aid. From the meager reports on the origin of these vessels in the work of Martin<sup>5</sup> and of Lewis<sup>6</sup> it appears that they arise after the swellings have been hollowed out to form the semilunar valves and therefore after the separation of the aorta and pulmonary artery is complete. Whether they arise from behind the different cusps or from the same sinus of Valsalva appears to depend more upon the location of the cusps with reference to the respective courses of these arteries in the heart, rather than to the sinus from which they normally take origin. If the opening between the valves has a more antero-posterior direction they arise from different sinuses; if the opening is more nearly in the coronal plane they take origin from behind the same cusp, namely the anterior.

In cases in which the cusps are of unequal size it appears probable that the anomaly may have resulted from fusion of two cusps which were fully formed and therefore after complete separation of the common trunk into the aorta and pulmonary artery. In those instances in which the valves are of approximately equal size, it is more likely that the malformation occurred before the separation of vessels, or at the time of the division by fusion of the two halves of the right and left lateral swellings.

The separation of the aorta and pulmonary artery and their opening into the left and right ventricles is completed by the union of the descending partition of the common vascular trunk with the partition (the membranous or "unprotected" part of the inter-ventricular septum) formed from the two proximal swellings. This partition is then continued downward in a direction from the right, above and behind to the left and downward and forward. Mean-

<sup>5</sup> Compt. rend. Soc. de biol., Paris, 1894, 6, 83.

<sup>6</sup> Anat. Anzeiger, 1904, 25, 261; Jour. Anat. and Physiol., 1904, 3, 12.

while the interventricular septum has been growing upward somewhat more nearly in the sagittal plane but deviating slightly to the left. The descending intervacular partition and the ascending interventricular septum meet, therefore, at an angle. The completed partition which separates the two ventricles and brings each of the two main arterial trunks into relation with its proper heart chamber, is, therefore, made up of three parts, namely, the partition of the trunk itself, that formed from the proximal swellings, and the interventricular septum. It is evident that complete and proper closure of this septum must depend upon all of these parts progressing in their normal directions. A shifting of the direction of any one or more of these parts makes possible the production of a malformation, either of the valves or of the interventricular septum or of both. Hence malformations of the aortic or pulmonary valves due to maldirection of the descending partition in the common trunk would show a greater tendency to other malformations of the heart, than those resulting from maldevelopment of the distal swellings or to fusion of two swellings or of two fully-formed cusps. In view of the above considerations it appears probable that the reduction in the aortic cusps in Case II originated at the time of or subsequent to the separation of the aorta and pulmonary artery, and that it was the result of some factor other than maldirection of the descending septum in the common vascular trunk.

TABLE III. OTHER MALFORMATIONS OF THE HEART ASSOCIATED WITH MALFORMATIONS OF THE AORTIC AND PULMONARY VALVES.

	Aortic.		Pulmonary.		Totals.
	2 cusps.	4 cusps.	2 cusps.	4 cusps.	
Defect in interventricular septum . . . . .	0	0	30	2	32
Patent foramen ovale <sup>1</sup> . . . . .	2	0	0	0	2
Patent ductus arteriosus <sup>2</sup> . . . . .	4	1	0	0	5
Defect of interventricular septum with patent foramen ovale . . . . .	1	0	25	0	26
Defect of interventricular septum with patent ductus arteriosus . . . . .	0	0	8	0	8
Defect of interventricular septum with patent foramen ovale and patent ductus arteriosus . . . . .	1	0	11	0	12
Totals . . . . .	8	1	74	2	85
Total number of cases of malformation of the semilunar valves . . . . .	56	5	88	46	195
Percentage of malformation of semilunar valves associated with other malformations of the heart . . . . .	14.3%	20%	84.1%	4.4%	

<sup>1</sup> Of the 2 cases with patent foramen ovale, 1 was five hours old, the other thirty-four years old.

<sup>2</sup> Of the 4 cases with patent ductus arteriosus, the ages were ten weeks, three and a half months, and three years (2 cases).

It has already been mentioned that the anomaly of two cusps in the pulmonary valve is very frequently associated with other malfor-

mations of the heart. The frequency with which other malformations occur in association with anomalies of the aortic and pulmonary valves is shown in Table III, based on 195 cases collected from the literature.

From this table it appears that about 84 per cent of cases with two cusps in the pulmonary valve are associated with other more serious malformations of the heart, as compared with only about 14 per cent of those with two cusps in the aortic valve. It is further evident that the malformations found with two semilunar valves in the pulmonary artery are of very grave nature, such as a defect in the interventricular septum, while the majority of those associated with two aortic cusps are less serious, such as patent foramen ovale (which is frequently closed by a valve-like flap) or a patent ductus arteriosus. The greater seriousness of the malformation by reduction in the number of pulmonary cusps is further shown by an analysis of the age at death of 150 cases collected from the literature. This is shown in Table IV.

TABLE IV. PERCENTAGE OF DEATHS UNDER TWENTY YEARS OF AGE WITH MALFORMATIONS OF THE AORTIC AND PULMONARY VALVES.

Lesion.	Total cases with age given.	Deaths under twenty years.	Per cent.
2 aortic valves . . .	44	17	38.6
4 aortic valves . . .	5	0	0.0
2 pulmonary valves . .	76	65	85.5
4 pulmonary valves . .	28	7	25.0
	<hr/> 150	<hr/> 88	

The facts presented in Tables III and IV strongly suggest that the mechanism of formation of two cusps in the pulmonary valve may be different from that of the production of two cusps in the aortic valve. de Vries concluded that this anomaly of the pulmonary dated prior to the separation of the common vascular trunk into the aorta and pulmonary artery, and that the corresponding anomaly of the aortic valve arose after that embryonic period. The above analyses indicate that this is probably true. Or at least that the reduction in the number of pulmonary valves results in the majority of cases from maldirection of the partition which divides the common trunk, while reduction of the aortic valve results from fusion of two cusps, either after the complete separation of the two large vessels or at the time of this separation by the fusion of the two halves of the right and left distal swellings which subsequently becomes hollowed out into one cusp.

Babes,<sup>4</sup> Thorel,<sup>7</sup> and Herxheimer assert that malformed heart valves are more susceptible to endocarditis than are normal valves. This may be true, but from an analysis of 192 cases collected from

<sup>7</sup> *Ergebn. d. allg. Path. u. Anat.*, 9, 602; 17, 360.

the literature it appears that there is a difference in the susceptibility of the different types of malformed aortic and pulmonary valves to infection. This is shown in Table V.

TABLE V. CASES SHOWING EVIDENCE OF ENDOCARDITIS (USUALLY CHRONIC) OF MALFORMED AORTIC AND PULMONARY VALVES.

Lesion.	Total number cases.	Number of cases with endocarditis.	Per cent with endocarditis.
2 aortic cusps . . .	55	23	52
4 aortic cusps . . .	5	1	20
	<hr/>	<hr/>	<hr/>
	( 60)	(24)	(40)
2 pulmonary cusps . .	88	21	24
4 pulmonary cusps . .	44	0	0
	(132)	(21)	(16)
	<hr/>	<hr/>	<hr/>
Totals . . . . .	192	45	23

From Table V it appears that the incidence of chronic and acute endocarditis occurs in a much larger percentage of cases with two semilunar valves in the aorta and pulmonary artery than in cases with four cusps. This is especially true of the pulmonary artery. The number of cases of four cusps in the aortic valve is too small to justify considering the 20 per cent of cases with endocarditis as anything like accurate. Endocarditis of the aortic valve is from thirty-five to forty times as common as in the pulmonary valve in cases with the normal number of cusps. Twenty-four per cent of the collected cases of pulmonary valves with two cusps showed endocarditis; while 42 per cent of two cusp aortic valves showed this lesion. It appears, therefore, that reduction in the number of pulmonary semilunar valves is not only very commonly associated with other serious malformations of the heart, but also that this anomaly causes a greater predisposition to endocarditis in this valve than the corresponding malformation does in the aortic valve.

**Summary.** Two cases of congenital malformation of the aortic and pulmonary valves are reported and the possible and probable mechanisms by which the anomaly developed have been discussed. Reduction in the number of semilunar valves in the pulmonary ostium is the most serious malformation of these valves because it is so frequently associated with other more grave malformations of the heart, especially with defect of the interventricular septum. Malformation of the aortic and pulmonary valves predisposes to endocarditis; this is more marked in the pulmonary than in the aortic valve.

## REVIEWS.

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MODERN ASPECTS OF THE CIRCULATION IN HEALTH AND DISEASE.

By CARL J. WIGGERS, M.D., Professor of Physiology, Western Reserve University. Second edition. Pp. 662; 204 illustrations. Philadelphia and New York: Lea & Febiger, 1923.

A COMPARISON of the present edition of this monograph with that published eight years ago, reveals most strikingly the enormous amount of research on problems of the circulation that has been published in that short time. The text has been thoroughly revised, amplified, brought up to date and several new chapters added, with the result that the present edition is almost twice the size of the first. The general arrangement of the first edition is retained. There are three main sections, the first dealing with modern conceptions as to how the circulation is maintained in health, the second, with various instruments and procedures which are available for studying the circulation in man, while in the third "the effort has been made to correlate the data obtained by experimental investigation of the abnormal conditions in the laboratory with the results derived from the application of instrumental methods at the bedside and then to relate these in turn with the simpler signs and symptoms of the clinic."

The author has made many important contributions to the study of the circulation, and there is perhaps no one in this country better fitted to write a book on the circulation. The difficult and complex subject is dealt with in a manner that compels admiration. There is no other book to compare with it in the English language. The reviewer devoutly wishes that some of the writers who deluge clinical literature with their notions of cardiac function, blood-pressure and various other problems relating to the circulation, might be compelled to cease writing until they had read and digested the contents of this volume.

One hesitates to criticize adversely in any way so fine a work, yet it should be pointed out that the discussions of the clinical manifestations of the various diseases of the circulatory apparatus add little to the value of the book, and in the opinion of the reviewer, might well have been omitted. The best that can be said of them is that they are well done, considering the fact that they were done by a physiologist.

W.

THE HEART IN MODERN PRACTICE. By WILLIAM DUNCAN REID, A.B., M.D., Chief of Heart Clinic at the Boston Dispensary. Pp. 352; 33 illustrations. Philadelphia and London: J. B. Lippincott Company, 1923.

THE author states that he has attempted to fill the need for a book incorporating the best of the new knowledge with that less recently acquired, and at the same time brief enough to be attractive to the bulk of the profession. The doctrine presented is, for the most part, orthodox, the author's style is attractive and it may be fairly said that he has accomplished what he set out to do. However, the book is not without faults. There is too much repetition in regard to the cardiac arrhythmias. The discussions of tests of heart function and roentgen-ray examination are inadequate. Recent contributions to hematorespiratory physiology throwing light on the symptoms of heart disease are almost entirely ignored. The chapter entitled "Septic Heart Disease" is out of line with present-day views; the various clinical types of bacterial endocarditis should be differentiated. It is distressing to encounter the statement that septic heart disease is really a form of rheumatic heart disease. The case-reports appended add little or nothing to the value of the book.

W.

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THE DOCTOR LOOKS AT LITERATURE. By JOSEPH COLLINS. Pp. 317; 12 illustrations. New York: George H. Doran Company, 1923.

THERE are both good and evil ingredients in this mixture of the so-called psychological aspects of recent literature. The different sections are bound together only by their having a common psychological interest. Unfortunately, however, the emphasis is laid to such an extent on sex matters as to make the book of doubtful value. In the first chapter Dr. Collins writes, "For a time it seemed to the casual observer that the new psychology was so steeped in pruriency that it could not be investigated without armor and gas mask." Unfortunately the extracts which Dr. Collins has chosen to quote from the works of Lawrence and others make it seem that his statement is still true today. Anyone who wishes to learn of such books will find a number of suggestions in the present volume. On the other hand, Dr. Collins discusses most entertainingly a number of books and authors who are not open to this criticism. The reviewer is delighted to find high praise of *Bunker Bean* and *Barbellion's Diary*, two favorites of his own. On the whole the book is enjoyable and well written and might be highly praised except for the one serious fault emphasized above.



CLINICAL SYMPTOMATOLOGY OF INTERNAL DISEASES. PART II. GENERALIZED PAIN. By PROFESSOR DOCTOR NORBERT ORTNER. Translated by FRANCIS J. REBMAN. Pp. 596. New York: Medical Art Agency, 1922.

THE author enumerates the various disease conditions that may give rise to pain in a given locality and discusses differential diagnostic factors. Chapters are devoted to precordial pain, chest and back pain, pain in the head, neck and extremities. Abdominal pain has been treated in another volume. While the book contains an enormous amount of really valuable clinical information, the material is not presented in a readily available form. A better book make-up with more chapter subdivision and adequate headings for each part would have obviated much of this difficulty. As a further handicap there are many grammatical errors, incorrect English idioms, and words poorly selected, at times improperly used, at times coined by the translator: sensible for sensory; pectoral for thoracic; anonymous for innominate; cucullaris for trapezius; yelegt, causating, coronaritis, frustaneous, etc.

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FEEDING, DIET AND THE GENERAL CARE OF CHILDREN. By ALBERT J. BELL, A.B., M.D., Assistant Professor of Pediatrics in the Medical Department of the University of Cincinnati. Pp. 276; 11 illustrations. Philadelphia: F. A. Davis Company, 1923.

IN this book, which is intended for the use of mothers and nurses, much of the subject-matter is evidently drawn from the author's own experience. The sample diet lists for the first twelve years of life and the chapter on "Dentistry" should prove helpful to the reader. On the whole, however, there is little if any material not already found equally well arranged in other books on this subject; not enough that is valuable, in fact, to compensate the reader for the poor style and careless use of the English language which exists throughout.

A.

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THE VITAMINS. By H. C. SHERMAN, Professor of Food Chemistry, Columbia University and S. L. SMITH, Specialist in Biological and Food Chemistry, United States Department of Agriculture. Pp. 273; 20 illustrations. New York: The Chemical Catalogue Company, 1922.

THIS valuable book is one of The American Chemical Society Series of Scientific and Technologic Monographs. The develop-

ment of knowledge in all branches of science has been so rapid in recent years that it is difficult for any individual to keep in touch with the progress of subjects outside of his own specialty. These monographs, therefore, perform a service of the highest value, prepared as they are by recognized authorities in their particular field, who have gathered, coördinated and presented in concise and readable form the knowledge available upon a single topic. The authors have succeeded well in performing this task for the vitamins. While the book is particularly valuable to those interested in food chemistry, the chapter on "Vitamins in the Problem of Food Supply" is catholic in its appeal. Our knowledge of vitamin distribution in foods and their significance in nutrition is adequate to make possible an intelligent use of food so as to provide for our vitamin needs, and without going beyond the range of ordinary staple articles of diet. There is appended a very complete bibliography with over nine hundred references. K.

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ENDOCRINE GLANDS AND THE SYMPATHETIC SYSTEM. By P. LEREBoullet, P. HARVIER, H. CARRION and A. G. GUILLAUME. Translated by F. RAoul MASON, M.D., Instructor in Pediatrics, New York Postgraduate Medical School and Hospital; Assistant Attending Physician, Willard Parker Hospital; Assistant Pediatricist, New York Postgraduate Medical School and Hospital Outpatient Department. Pp. 378; 31 illustrations. Philadelphia: J. B. Lippincott Company, 1922.

In a lengthy but interesting introduction, the writer sketches the achievements and problems of endocrinology. Harvier then takes up the pathology of the endocrine glands and the resultant disease pictures. This section, while fairly well done, is inadequate. For example, basal metabolism in thyroid disease is never once mentioned in the text and is deemed worthy of only a three-lined footnote by the translator. Roentgen-ray treatment of hyperthyroidism is discussed in four lines. The failure to mention the work of Kendall on thyroxin, of Marine in endemic goiter, of Wilson on alkalosis in tetany is further evidence not only of incompleteness but of provincialism. Guillaume, writing on the vegetative nervous system, contributes a very interesting chapter, that is, however, handicapped by the unfortunate shortcomings of the translator, whose command of English is evidently not up to his French. In addition to the frequent use of French idiom literally translated (the pulse is weak the urines rare), and English words wrongly used or improperly compounded, he has increased the difficulties by not conforming strictly to current anatomical terminology. There is a chapter by Harvier on the pathology of

the greater sympathetic and a concluding chapter (brief, sketchy, unconvincing) on organotherapy by Carrion, the burden of which may be gathered from this quotation: "Every time that an organ is functioning deficiently the indication is to administer the extracts of a corresponding organ"—(liver, kidney, brain, stomach, etc.). The book can scarcely be considered a valuable addition to the English literature on endocrinology. K.

**MULTIPLE SCLEROSIS (DISSEMINATED SCLEROSIS).** An Investigation by the Association for Research in Nervous and Mental Diseases. Pp. 241. New York: Paul B. Hoeber, Inc., 1923.

THIS monograph is a compilation of the papers and discussions of the 1921 meeting of the Neurological Association. The papers by eminent neurologists are edited under the following headings: I. General and Historical Considerations. II. General and Special Symptomatology. III. Differential Diagnosis, Course and Treatment. IV. Pathology. V. Bibliography. At the close of each chapter are the conclusions of the commission. In general, this monograph covers the subject more completely than any previous works. Much that is new is presented in the statistical study of the disease, both in civil life and in the late war. About sixty pages are taken up by symptomatology. Extensive studies on bacteriology, serology and blood and spinal fluid chemistry are included. The latest work on the histopathology of multiple sclerosis, with excellent illustrations and cases are offered. There is a long bibliography at the end. The volume is not indexed.

B.

**NERVE EXHAUSTION.** By MAURICE CRAIG, C.B.E., M.D. (CAN-TAB), F.R.C.P. (LONDON), Physician for and Lecturer in Psychological Medicine, Guy's Hospital. Pp. 148. Philadelphia and New York: Lea & Febiger, 1922.

THE book is mainly divided into five chapters. The chapter on "Causation" covers the subject from the etiological standpoint very thoroughly. Under "Symptomatology," the author departs from the subject of nerve exhaustion *per se* and enters the realm of the psychoses, with all their attending characteristics, failing to differentiate between those states which are purely exhaustion phenomena and those in which we have discovered no etiology. The premise that all forms of psychoses, except the organic, are on an exhaustion basis is not proved.

A special chapter is devoted to "Sleeplessness" and the subject is very well handled. The remaining chapters on "Diagnosis and Prognosis," and "Treatment" are valuable from the viewpoint of the general practitioner, as well as the neuropsychiatrist.

On the whole, not enough stress is laid on somatic conditions accompanying nerve exhaustion phenomena. Psychoanalysis is very conservatively treated in this book, and on page 122 the author states "We do not believe that sexual conflicts and suppressions are of necessity the cause of psychoneuroses, and the experience of the writer is that many patients who have been analyzed by recognized exponents of the Freudian school have been made infinitely worse by the conclusion that their malady is sexual or homosexual in origin, and after all it is a pure hypothesis which, although, as we have admitted, true in a certain number of cases, is by no means so proved as to enable it to be regarded as universal." On page 126 he further remarks that "Whilst bearing in remembrance the great importance of mental conflict, repression and dissociation, as physicians we must not forget that after all the problem of nerve exhaustion is one in which almost every system of the body may have become involved, and therefore the treatment must not be narrowed down to fit any one theory," with which the reviewer agrees entirely.

The book is well written, the diction is easy and, with the exception that the reader may be confused between psychoneurotic phenomena and certain psychoses, it is clear and instructive.

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DISEASES OF THE GUMS AND ORAL MUCOUS MEMBRANE. By SIR KENNETH GOADBY, K.B.E., M.R.C.S., L.R.C.P., D.P.H. (CANTAB.), Lecturer on Bacteriology of the Mouth, Dental Department, University College Hospital, etc. Pp. 383; 106 illustrations and 8 colored plates. London: Oxford Medical Publications, 1923.

THE author by no means limits himself to the subjects indicated by the title. In addition to a description of the various forms of gingivitis, ulcerations of the gums and diseases with peculiar oral symptoms, there are chapters devoted to alveolar abscess, pyorrhea alveolaris, neuralgia and mouth neuroses and examination and interpretation of radiographs of the jaw. It is difficult to see a close connection between some of these subjects and diseases of the mucous membrane except as a matter of differential diagnosis. Curiously enough, some of these irrelevant chapters are among the best in the book. Worthy of particular mention is that on disease originating from mouth affections, to which an extensive bibliography is appended. We are unacquainted, how-

ever, with the "Section of Orthodontic Surgery of the American Medical Association," referred to on page 137. As might be expected from the eminence of the author as a bacteriologist, the sections dealing with the bacteriological aspects of mouth disease are especially commendable, as also are those on lead and bismuth poisoning. One cannot help feeling that had the author more strictly limited himself to the gums and mucous membrane proper, a more notable contribution would have resulted. T.

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NURSERY GUIDE FOR MOTHERS AND NURSES. By LOUIS W. SAUER, M.A., M.D., Senior Attending Pediatrician, Evanston Hospital; formerly Attending Physician, Chicago Infant Welfare; Assistant Attending Physician, Children's Memorial Hospital, Chicago. Pp. 187; 12 illustrations. St. Louis: C. V. Mosby Company, 1923.

MOTHERS and nurses will find this a very valuable assistant in the daily care either of the sick or of the well infant. The tables, such as that giving the number of tablespoonfuls of various powdered foods or cereals to the ounce, are especially practical. The arrangement of the index and subject-matter renders rapid reference convenient and will give a feeling of comfort to the mother who may need immediate aid in illness or accident before the doctor comes. A.

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CLINICS AND COLLECTED PAPERS OF ST. ELIZABETH'S HOSPITAL, RICHMOND, VA. VOLUME OF 1922. Contributed by the STAFF. Pp. 560; 218 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS book consists in a collection of clinics and papers by the staff of St. Elizabeth's Hospital, Richmond, Va. The excellent illustrations by Helen Lorraine and the numerous photographs are notable features of the work, while contributions by J. Shelton Horsley, Warren T. Vaughan, Austin I. Dobson and Fred M. Hodges compose the major part of the book. Publications of this kind are of distinct value, and it is to be hoped that the annual issues of the *Clinics and Collected Papers of St. Elizabeth's Hospital* will maintain the same high standard which they have set in this, the first volume. A.

# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

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AND

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**Pernicious Bothriocephalic Anemia in Three Sisters.**—A. CRAMER (*Bull. et mém. Soc. méd. d. hôp. de Par.*, 1922, 38, 1475) reports an anemia of the pernicious type, associated with infection with *Dibothriocephalus latus*, in three sisters, two of whom succumbed to the disease. In all three, there was a severe anemia, the red cell counts being 1,700,000; 540,000 and 806,000 respectively, on admission to the hospital. There were nucleated red cells, including megaloblasts, anisocytosis and poikilocytosis. There was also a leukopenia in 2 cases (3100 and 3600 leukocytes per cmm), while in the patient who recovered the white counts shortly after admission were 7700 and 9300, with a practically normal differential count, except for the presence of an occasional myelocyte. An eosinophilia is not recorded in any of the cases. One sister, aged thirty-five years, died three days after admission; at autopsy three well preserved specimens of *Dibothriocephalus latus* were found in the small intestine. Hemosiderosis of the liver and kidneys, sub-pericardial, subendocardial and esophageal ecchymoses, and fatty degeneration of the heart muscle were observed. The second sister, aged thirty-eight years, died the sixth day after admission. Before death, two living worms were expelled from the intestines. In the patient who recovered (red cells 806,000; white cells 7700 on admission), the parasite was probably passed shortly before she entered the hospital, since many ova were found in the stools, but neither proglottids nor parasite were passed after vermifuge. The patient made an uninterrupted recovery. For several years the three sisters had occupied a single room, which they seldom quit, and slept in one bed. Their nourishment had consisted entirely of preserved foods. This unhygienic mode of living undoubtedly lowered their resistance. The cases are of interest because of the apparent increase in the United States of

infestation with this parasite, and also because they seem to refute the theory that anemia develops in infested individuals only after the death of the parasite. In both of the author's fatal cases of bothriocephalic anemia, there was no evidence of dead tapeworms in the intestine.

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**Pathological Amino-aciduria.**—S. ZANDEÉN (*Ztschr. f. klin. Med.*, 1922, 94, 101) has made a study of the amino-acids in the urine, using the formalin titration method of Sørensen. His conclusions are mainly as follows: (1) In marked icterus a normal excretion of amino-acids points to a stagnation of bile, while an increased excretion of acids indicates hepatitis in addition to stagnation. The method can also aid in the early diagnosis of a hepatitis or of a liver atrophy in cases where the clinical symptoms seem to indicate a catarrhal jaundice. (2) In pulmonary tuberculosis, a determination of the amino-acids in the urine gives a better indication of the state of the liver than palpation and percussion of the organ. (3) In hepatic cirrhosis, a pathological amino-aciduria appears first in the terminal stages of the disease, when the clinical symptoms indicate a contracted liver.

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**Recent Progress in Our Knowledge of Parasitic Worms and Their Relation to the Public Health.**—NICOLL (*Parasitology*, London, 1922, 14, 378) publishes a review of the important advances in parasitology of the last ten years, together with references to the literature up to the end of 1921, with a few of more recent date. Of the facts brought out by the author, only a small number can be referred to here. Of importance to American tourists intending to visit the Nile are Leiper's conclusions on the prevention of bilharziasis. He showed, among other things, that infection in towns is acquired from unfiltered water, which, in addition to filtered water, is still supplied, even in Cairo, though here it is delivered by a separate system of pipes. The occurrence of pneumonia in helminth infections has been brought into much prominence by recent work in connection with ascaris infection. Both Ransom and Stewart have definitely concluded that pneumonic symptoms are a regular concomitant of ascaris infection. In fact, Stewart regarded the onset of such symptoms in his experimental animals as definite evidence that ascaris infection had taken place. Ransom, moreover, associates the pneumonic disease, known as "thumps" in young pigs, with ascaris infection and by analogy suggests that many cases of pneumonitis in human beings, particularly children, are possibly the result of invasion of the lungs by infecting ascaris larvæ. Many other matters of great medical interest are reviewed, among which may be mentioned flies as carriers of parasitic infection, the occurrence of nematodes of the genus *Trichostrongylus* as human parasites, the route of invasion in ascaris infections and so on.

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**Ankylostoma Braziliense.**—LANE (*Ann. Trop. Med. and Parasitol.*, 1922, 16, 347) offers evidence to prove the identity of *A. braziliense* and *A. ceylonicum*, both of which have been encountered in man, the former being found first in Brazil, the latter in material from Ceylon. In a recent report (*Ibid.*, 1922, 16, 223) the author reports finding *A. braziliense* in man in 4 of 64 autopsies performed in Manaus, Amazonas, Brazil.

## SURGERY

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UNDER THE CHARGE OF

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**Diverticulum of Bladder.**—BALL (*St. Bartholomew's Hosp. Repts.*, 1923, 56, 159) says that diverticula of large size are relatively uncommon lesions. They exist both in the presence of and without obstructive lesions in the urethra or bladder. In both cases they probably have the same origin. Some defect in the bladder wall, either a gap in the musculature or a deformity resulting from the persistence of a portion of the urachus or an accessory ureteric bud. They seldom give rise to symptoms within the first three decades of life and then either from retention of urine or infection. Stone formation is a common complication. Radical removal is the only satisfactory method of treatment and preferably by extravesical excision. Palliative methods of treatment should be reserved for those cases in which a radical operation is contraindicated.

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**Mercury Inhalation Therapy of Syphilis.**—GUTMAN (*Am. Jour. Syph.*, 1923, 7, 326) says that evidence is submitted to prove that the respiratory tract is a desirable route for the administration of all drugs effective upon the general organism, especially mercury, because the absorption area of the respiratory tract is enormous, many times greater than the external surface of the body. The very dense capillary network of the pulmonary tissue and its immense quantity of blood, renewed more frequently than that of the other capillaries, favors immediate transportation of absorbed vapors. The very thin partition between vapors in the alveolar spaces and the blood in capillaries favors rapid diffusion. The ready vaporization, the nascent state and the peculiar molecular construction of mercury, all favor rapid diffusibility, absorption and effectiveness. Physiological data has been offered to prove that inhaled mercurial vapor is absorbed almost entirely from the respiratory and not the gastro-intestinal tract. Moreover, evidence has been offered which proves that inhaled vapors are not toxic or harmful to the respiratory tract.

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**The Surgery of Ectopic Kidneys.**—CAULK (*Ann. Surg.*, 1923, 77, 63) says that there are two main types of dystopic kidney: The single ectopic kidney, usually situated over the sacral promontory with the other kidney in normal position; while the second type is the fused ectopic kidney, extremely rare in occurrence, with definite fusion of renal tissue. The renal pelvis varied markedly in size and shape with short ureters. The single ectopic kidneys in the author's series



all showed infection. All were associated with bladder symptoms. Three cases showed large hydronephroses, which is a condition quite common in such kidneys. Another showed a tuberculous renal occlusion. Several of the cases which were thought to be abdominal conditions show the importance of urinary examination, but urinalysis gave the first clue to the true nature of the lesion. Streater lays down the following rules of dealing with ectopic kidneys in pregnancy: If discovered at beginning of pregnancy, laparotomy, dislocation or fixation should be done; if discovered later, the advisability of the induction of premature labor should be considered; a normal kidney should not be removed shortly before or during labor; if discovered after labor has begun a pathological kidney may be punctured to allow delivery and a nephrectomy done later.

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**Etiology of Varicose Veins.**—NICHOLSON (*Arch. Surg.*, 1923, 7, 47) says that since the saphenous vein opening into the femoral is always protected by two or more valves and the saphenous wall must at least intermittently bear the weight of the contained column of blood, it appears that the primary cause for varicose veins is not valvular insufficiency and static pressure. The infrequency of varices in the arms, where the weight of the column of blood in the veins is from a level only a little above the elbow, proves that static pressure is a secondary factor. Similarly, the relatively less severe process in the upper saphenous as compared with lower levels support this conclusion. The primary cause may be mechanical, trophic, inflammatory or toxic. Valves in the veins of the legs do not relieve the vessel walls of static pressure exerted by the contained column of blood. The chief functions of the valves are to aid the muscles as they contract in pumping the blood toward the heart, to direct the blood toward the heart, to prevent blood from being forced backward by intermittent muscular or mechanical pressure.

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**The Clinical Pathology of Pyloric Occlusion in Relation to Tetany.**—MURRAY (*Arch. Surg.*, 1923, 7, 166) says that with stenosis of the pylorus, hydrochloric acid cannot pass into the intestines and be reabsorbed. It is expelled by vomiting or washed out by gastric lavage. The result is a disturbance of the acid base balance in the blood tissues. The blood findings in the author's patients were similar to those in dogs after experimental pyloric occlusion, namely an increased carbon-dioxide and urea and a diminished chloride content. There is almost certainly a relationship between the recorded blood changes, and the condition of tetany that may develop in severe cases. It is considered by the author from his cases, experiments and laboratory findings that nerve irritation is increased by a fall in the hydrogen-ion concentration of the blood or by a rise in the sodium-calcium ratio. The treatment of gastric tetany is operative. It is always the result of obstruction of the pylorus, due to gross pathological changes.

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**Recent Progress in the Treatment of Chronic Empyemas.**—HEDBLUM (*Northwest Med.*, 1923, 22, 115) says that faulty drainage in acute empyema seems by far the most common cause of chronic empyema. The opening may be too high and too far forward, so that dependent

drainage is not secured. Secondarily infected tuberculous empyema is fairly common and is the most persistently chronic of all types. Lost drainage tubes and the possibility of the presence of sequestered fragments of denuded rib stumps are probably less often recognized. Constitutional diseases, such as syphilis, anemia, nephritis and amyloidosis give same clinical characteristics noted in secondary tuberculous cases. The only procedure representing a conservative type of surgery was the little used decortication operation. The more conservative methods of non-operative treatment, such as attempted sterilization of the cavity by the injection of formalin in glycerine, were regarded as of very limited application. The recent introduction of hypochlorite solution irrigation, has made possible the cure of some of these patients who can thereby be rendered good surgical risks. Dakin specified that the solution should be between 0.45 and 0.5 per cent in free chlorine content.

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**Carcinoma of Floor of Mouth.**—QUICK (*Am. Jour. Roentgenol.*, 1923, 10, 461) says that carcinoma of the floor of the mouth is a distinct clinical entity with peculiar therapeutic problems, which render it unlike any of the other intraoral groups. It is the belief of the author from this experience to date that interstitial radiation by means of unfiltered radium emanation tubes is the agency of choice in treatment of the primary lesion. The problem of dealing with the metastatic extension of disease to the cervical nodes is best handled on a conservative basis, using a combination of surgery, radium and roentgen-rays.

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## PEDIATRICS

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UNDER THE CHARGE OF

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**Consideration of the Causes of Stillbirths and Neonatal Deaths.**—BAILEY (*Arch. Pediat.*, 1923, 40, 226) says that certain facts stand out in the consideration of the deaths in the two clinics under his observation. First, in the adjoining districts covered by these institutions syphilis and toxemia play a minor part as a causation of fetal and neonatal death. Undoubtedly this is due to the close control of these patients in the prenatal clinics. Their efforts in prenatal care heretofore have been directed largely toward the correction of these two etiological causes and now, having been successful in a regime which does alter this factor, it would seem as if we must turn our efforts into another line. Another impressive fact concerning this study is that from an operative standpoint there is still a field for improvement. The direction that this must take has been shown to be better skill in delivering mothers by operative measures. The prevention of prematurity and the care of the premature in the neonatal period offer new problems, and in a field almost untouched and apparently one in which we might accomplish a great deal. In the first place these women must come to the prenatal clinics earlier in pregnancy, and it must be clearly under-

stood that possibilities of disaster as regards the fetus are as great in the seventh and eighth months of pregnancy as at term. There is a question as to the value of the nursing prenatal care as at present conducted. It seems more to the point to have this work conducted by well-trained physicians for the solving of this difficult and intricate problem. The probabilities are that more will be accomplished by a thorough social service nursing regime and by the patients' being brought into the clinic much more frequently to see the physician than is now the custom. In those instances where the patient is unable to come because of illness, she should be visited by a physician from the clinic or removed to the hospital. Those patients showing a trace of albumin in the urine must be considered as abnormal and their metabolism should be studied in the most thorough manner. A laboratory should be established in every prenatal clinic and a hospital should be supplied where such studies may be conducted. While it is impossible to consider the hospitalization of the majority of these women, rest and freedom from exertion should be provided by admitting to their homes prenatal workers of the mothers' aid type, so that the general housework may be lifted for them. The premature infant should be looked after by the trained pediatrician. Some of the most difficult problems in physiological and pathological aspects present themselves in this group, and these infants are at present cared for by the obstetricians, whose minds must be filled by the problems of pregnancy and labor. The association of the obstetrician and the pediatrician should be a close one, but the entire charge of the newborn child, whether premature or not, should be in the hands of the latter. This ideal arrangement is already working in some institutions. If the obstetrician has the amount of his work reduced in this way he may find time to investigate the conditions related to the production of premature birth.

**A Clinical and Roentgen-ray Study of Tuberculous Broncho-adenopathy.**—FRAZER and MACRAE (*Jour. Am. Med. Assn.*, 1923, 80, 1292) indicate that in the picture of the chest that the contour should be symmetrical, the trachea in the midline bifurcating in front of the body of the fourth dorsal vertebra or a little lower. The mediastinal shadow shows the heart to be more nearly transverse than in the adult, and in the very young the thymus shadow is sometimes recognized about the aortic arch when no symptom of enlarged thymus exists. The domes of the diaphragm are smooth and the right diaphragm is in front of the eighth interspace and the left is slightly lower. The hilum or root shadow is located in the inner zone and extends upward to about the fifth rib posteriorly and downward until it crosses four ribs and intervening spaces. Its width and density vary greatly in health. The lung fields show no markings in the outer zone and in the very young in the middle zone. At birth lung markings, as trunk shadows, are absent and the hilum shadow is small. As the child gets older, dust inhalations and infections make far more distinct shadows. The hilum shadow is produced by lymph nodes, thick-walled bronchial tubes, blood-filled vessels and connective tissue binding them together, and these shadows increase in density and area whether a history of infections is obtainable or not. Lymphadenopathy becomes apparent after the common diseases of childhood, especially those which involve the respiratory tract, such as whooping-cough and measles; but it must

be remembered that the lymphoid tissues in children are peculiarly prone to infections, notable chronic appendicitis and diseased teeth and tonsils. These causes must be excluded before making a diagnosis of tuberculosis as the cause of large hilum shadows. There is a group presenting as its salient feature marked tracheobronchial lymph glands and another group in which the same hypertrophy is associated with calcification of glands. All of the first group gave a positive Pirquet reaction and had known tuberculous foci elsewhere in the body. Those with calcified glands occurred in cases in which tuberculous bone lesions were present, with the exception of one case of osteomyelitis which gave a negative Pirquet reaction. If the roentgenogram had been relied upon exclusively some faulty deductions might have been made, for all of these children were in good health so far as their chests were concerned. It is striking that all cases in which bone lesions existed showed marked calcification of hilar lymph nodes, and the question arises as to whether or not the calcification of these nodes necessarily indicates the presence of a tuberculous process.

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**The Transmission of Syphilis to the Second Generation.**—COOKE and JEANS (*Am. Jour. Syph.*, 1922, 6, 569) say that it is highly probable that all mothers of syphilitic children are infected, although occasionally mothers of syphilitic children have negative Wassermann reactions, and more often mothers of older syphilitic children have negative Wassermann reactions or weakly positive reactions. In all such instances the maternal infection is latent. A strongly positive Wassermann reaction in the mother does not mean that her infant will necessarily be infected, and consequently a syphilitic mother may bear a healthy child. When the mother's Wassermann reaction is positive with the cholesterolized antigen only, the chances are about 7 to 1 that the infant is not syphilitic. In most instances the father brings the infection into the family, although nearly 40 per cent of the fathers of syphilitic children have negative Wassermann reactions at the time when the children are examined. The male may therefore transmit the disease after his infection has become latent. Transmission to the third generation is possible but this is incapable of proof. Identical or single ovum twins born to a syphilitic mother are both infected or both escape the disease. Double ovum twins have the same fate as children of two successive pregnancies. Either, neither or both may be infected. Adequate treatment of the syphilitic mother during pregnancy will result in a non-syphilitic infant, if the treatment is instituted before the fetus is infected. Often a relatively small amount of treatment is necessary to accomplish this. Subsequent pregnancies are not protected unless treatment is continued. It is probable that where a mother becomes infected during pregnancy, the fetus is infected also, but the treatment of the mother may be followed by a milder infection in the infant or lessen the danger of a fatal infection *in utero*. Placentas of syphilitic infants show characteristic diffuse microscopical changes in 27 per cent of the cases. When such changes are present the infant later proves syphilitic in every instance. Syphilitic infants at birth have Wassermann reactions in the following proportion: 37 per cent negative; 18 per cent weakly positive and 45 per cent strongly positive. After the first few weeks or months all syphilitic infants have strongly positive reactions.

## DERMATOLOGY AND SYPHILIS

UNDER THE CHARGE OF

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**Infantile Eczema and Examination of the Stools.**—WHITE (*Arch. Dermat. and Syph.*, 1923, 7, 50) gives the following instructions for the management of infantile eczema (he has popularized in this country the crude coal-tar treatment of infantile eczema which has been one of the most valuable therapeutic measures ever proposed for the treatment of this condition): (1) The baby is not to be taken outdoors, but is to be kept in a room with a southerly or westerly exposure; the heat is to be turned on, the window to be open day and night and a screen to be so arranged that neither wind nor sun shall strike the baby. (2) When the baby is to be fed or bathed, or its clothes are to be changed, it is to be taken to an adjoining warm room and returned as soon as possible afterward; wet or soiled diapers must be changed at once. (3) Care must be taken that the baby is not too warmly dressed. Overheating congests the skin and consequently increases the itching, one of the great hindrances to a rapid cure; rubber diapers must not be worn. (4) If the baby shows any desire to scratch, the sleeves of the nightdress must be firmly attached with a strong safety-pin to the diapers. The widely advertised aluminum mitts can do much damage and the stiff elbow joint cuffs do not prevent the use of the straight arm as a scratcher. (5) No soap or water should touch the eczematized skin, but the unaffected portions of the body may and should be bathed daily with tepid starch water, and, if necessary, a superfatted cold-cream soap may be used. (6) No change in the diet is to be made at the first visit. (7) Night and morning, the following paste should be applied to the diseased skin, care being taken that the paste is black and never olive-green: Crude coal-tar and zinc oxide, 2 parts each; cornstarch and petrolatum, 16 parts each; the paste should be buttered on with a wooden throat stick and never bandaged; before each application, all remnants of the previous inunction should be removed with sterilized gauze wet with olive oil and the fresh ointment applied immediately afterward. In preparing the paste, the crude coal-tar should be rubbed up gently and persistently with the zinc oxide. This combination with the metal prevents the extraction of the crude oil from the tar. If this oil is separated from the mother substance, we have the mischievous, irritating olive-green mass which may produce a dusky erythema, pustules and possible toxic absorption, resulting in headache, malaise, nausea or vomiting and pyrexia. After the crude coal-tar and the zinc oxide have been well incorporated, the product should be passed through a fine sieve and rubbed up with the well-mixed cornstarch powder and petrolatum. In case the scalp is involved, we omit the cornstarch from the prescription. Do not hesitate to use this black ointment on the most excoriated and aggravated skin. If the eczema is a dry one, use 20 grains (1.3 gm.) of

crude coal-tar instead of the customary 30. The mother should be told that the resultant black stains can be removed from the clothes by thorough impregnation with lard, followed by washing with a pure hard soap and hot water. These instructions are to be followed to the letter for one week, and the child is then to be examined again. The author emphasizes the importance in the small group of cases which resist this treatment, of making a careful examination of the stools. Abnormal stools seemingly accompany every obstinate example of infantile eczema. Excessive fat occurs in 60 per cent; excessive starch in 40 per cent, excessive sugar in 20 per cent and excessive protein in 10 per cent. Rectification of the diet was attended by distinct success in a great majority of the cases. A considerable series is reported in detail and forms the basis for the author's insistence that properly performed stool examinations are a necessary part of the proper examination and treatment of children with infantile eczema.

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**Sulpharsphenamine.**—VOEGTLIN, JOHNSON and DYER (*Pub. Health Repts.*, November, 1922, p. 2783) discuss the preparation, chemical constitution and chemotherapeutic value of sulpharsphenamine. This drug has been used abroad under the trade name of "Sulpharsenol," prepared by a secret process. The new drug is much more stable than neo-arsphenamine, and its trypanocidal action definitely more marked. In its ultimate sterilizing power it closely approaches arsphenamine (606) itself. The drug is prepared from arsphenamine, formaldehyde and sodium bisulphite and differs from neo-arsphenamine by the presence in the side chains of one more atom of oxygen. The drug may be given intramuscularly in 30 to 40 per cent solution, without marked irritation, and its colloidal character is evidenced by the fact that in this concentration it forms a jelly. The trypanocidal action is reported by these investigators as distinctly slower but ultimately more complete. Spirochetes may not disappear from active lesions for more than twenty-four hours. The dose at present recommended is 4 ggm. every five days given intramuscularly. In a subsequent publication by VOEGTLIN, SMITH, DYER and THOMPSON (*Pub. Health Repts.*, 1923, 38, 1003), further studies of the penetration of the cerebrospinal fluid by arsenic in various organic arsenicals is reported. The authors introduced into the subarachnoid space of the rabbit active trypanosomes in a known concentration. Meningeal infection remains local long enough to test the efficiency of trypanocidal drugs by the intravenous route. In studying a number of preparations, including tryparsamide, sulpharsphenamine, arsacetin, neo-arsphenamine, arsphenamine and silver arsphenamine, it was found that from the standpoint of penetration of the meninges with sterilizing effect, arsphenamine, neo-arsphenamine, silver arsphenamine and some other compounds had a relatively low efficiency except in enormous dosage. Sulpharsphenamine proved to be the most effective arsenobenzol derivative. It compared favorably with tryparsamide and 3-amino-4-oxyphenylarsonic acid in penetrative power. Studies of the action of these drugs by this biological method indicate that the best results with any arsenical will probably be obtained by using single large doses approaching closely the maximum tolerated dose

and given a week apart, rather than by smaller doses at shorter intervals. Sulpharsphenamine used in the treatment of syphilis of the nervous system should be given intravenously (personal communication).

**The Diagnosis of Cardiovascular Syphilis.**—REID (*Boston Med. and Surg. Jour.*, 1923, 188, 189) finds that syphilis was present as the cause of cardiovascular disease in 11.5 per cent of 100 successive patients dying in the medical wards of the Boston City Hospital. He quotes Lamb who has estimated that 15 to 25 per cent of organic heart disease in a general hospital is syphilitic and that it is present in 50 to 75 per cent of patients affected by syphilis. The author points out that the first essential in the diagnosis of cardiovascular syphilis must be a wider recognition by the clinician of the fact that it is an important element to be considered in the diagnosis of all cardiac diseases. The history of a chancre is commonly denied. Too much reliance must not be placed upon the marital history as regards miscarriages, still-births or living children. The general examination should include a search for syphilis elsewhere in the body. Cardiovascular syphilis may be symptomless unless complications have ensued. If there be symptoms, pain and shortness of breath, both located by the patient as under the upper sternum, are most typical. The pain shows the radiation similar to that in angina pectoris. Enlargement downward and to the left and an abnormal supracardiac dulness are common. The most frequent murmur is a systolic one at the aortic area. The aortic second sound is often of a duller tone as in arteriosclerosis. There is nothing characteristic in the blood-pressure findings unless the complication of the aortic insufficiency has ensued. A positive Wassermann reaction is of value in supporting the diagnosis but a negative report is often received and should not be allowed to shake the diagnosis of cardiovascular syphilis if sufficient other data point to the presence of that disease. The roentgen-ray findings are often of great value, but may fail to detect early cases in whom only a tentative diagnosis may be possible. The therapeutic test for syphilis is of definite value in doubtful cases and should be more frequently used. Diagnosis cannot rest on any one point, but requires careful attention to all the factors in the case.

## OBSTETRICS

UNDER THE CHARGE OF

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**The Duration of Feeding by Nursing.**—(*Jour. Am. Med. Assn.*, 1923, 80, 113). An editorial upon this subject comments upon recent articles in which the rate of secretion of breast milk was studied. To secure

the best results for mother and child the question arises as to how long the nursing infant should be allowed to remain at the breast. If the total time is computed it may be found that considerable of the mother's attention is required for this purpose. If the mother be a wage earner or the head of a large household, this may become important. The usual tradition is that twenty minutes should suffice for each feeding, but SMITH and MERRITT (*Am. Jour. Dis. Child.*, 1922, **24**, 413) have studied this question by weighing infants at various periods of the nursing act. They found that from 40 to 60 per cent of the child's milk is obtained in the first two minutes, and from 60 to 85 per cent in the first four minutes. This is independent of the character of the supply, and whether it is abundant, moderate or scanty. Very few nursing infants get any milk whatever after eight minutes. These studies would indicate that a normal child gets enough milk from one breast if it nurses only from six to eight minutes, rarely from ten to twelve. From this it is reasoned that bottle-fed babies should not have a bottle more than ten minutes.

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**The Pelvic Fascias.**—FRANK (*Am. Jour. Obst.*, 1923, **6**, 8) contributes an illustrated article upon the treatment of cystocele, rectocele and uterine prolapse. This article is based upon his studies in the anatomy and pathology of the pelvic fascias. He finds that the bony pelvis is closed in by a bowl-shaped musculo-fascial diaphragm, which he calls the levator plate. In its anterior portion this diaphragm has an elliptical or genital hiatus, bordered laterally by the levator edges. This gap is partially closed and the diaphragm is reinforced by a strong fascia, the triangular ligament, which extends from one pubic ramus to the other. The urethra and vagina pierce the triangular ligament. The uterus, bladder and rectum are retained in their normal positions by strong yet elastic bands of connective tissue and unstriated muscle, most important of which are the parametria, pubo-cervical fascia, paraproctium and paracolpium. The pelvic diaphragm takes up exceptional and especially short, excessive strains and stresses. It is unable to support the pelvic viscera alone. The round ligaments and sacro-uterine ligaments possess little tensile strength and serve merely to tilt the uterus forward or backward. Injuries, resulting almost exclusively from childbirth, cause defects in the pelvic tissues followed by cystocele, rectocele and prolapse. When considering the question of intervention, careful selection of cases is necessary. No operation is required in many patients with minor injuries. Patients who are still bearing children may be treated by palliation, and old and debilitated patients must be so treated. In operating upon women in the age of child-bearing, plastic vaginal repair must not narrow this canal to excess, and the only operation justifiable for correcting retroflexion is the shortening of the round ligaments. Ventrofixation is indicated after the menopause or after sterilization. There is a close analogy between operation for the cure of abdominal herniæ and operation for the repair of cystocele and of high and low rectocele. To secure a good result it is essential that tears in the fascia are brought together and that the genital hiatus is permanently narrowed. It is only in exceptional cases that opera-



tion by vaginal interposition, vaginal hysterectomy and obliteration of the vagina should be performed. In discussion, Vineberg, like the writer, had been impressed by the importance of saving the cellular tissue surrounding the cervix uteri. In operating for rectocele he is accustomed to the denudation posteriorly almost to the cervix, making a wide denudation and passing the sutures so as to embrace the fascia externally, coming out on the opposite side at the point of entrance. Some cases of cystocele where the whole anterior vaginal wall prolapses he considered practically incurable. Taylor believes that many women in the child-bearing age who have lacerations should have these closed to avoid the injury to the general health and the progressive relaxation of tissues which they cause. Where patients are beyond the child-bearing age the plan of operation is not, strictly speaking, by interposition, but by replacing the bladder and retaining it in a position approaching the normal. Hysterectomy is rarely indicated for prolapse, and in women beyond the child-bearing age when plastic work is done, a firm fixation of the fundus of the uterus to the abdominal wall gives good results.

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**Hemorrhagic Lesions of the Placenta.**—McNALLEY and DIECKMAN (*Am. Jour. Obst.*, 1923, 57, 55) publish an illustrated paper upon this subject, giving the result of studies which they have undertaken to ascertain the relation between hemorrhagic lesions of the placenta and the formation of white infarcts. Such study is timely, for infarcts of the placenta are not unusual, and their significance is not always understood. The writers find that at least some of the usual white infarcts which are caused by changes in the villi may first be red in color. It is proper to apply to these the term "red infarcts." Other lesions that have received different names should not be called red infarcts because they are really not infarcts but collections of blood. It would be better to call these "hematoma" or "hepatization," and the choice of term would depend upon whether the lesion was circumscribed or diffused. They all have a common cause. The villi are nourished primarily by maternal blood. When collections of blood form in the placenta, white infarcts may begin in two ways. In one the blood itself is actually changed into a white infarct, which in its gross appearance does not differ from any other. In another sort of lesion the blood collected in the placenta causes infarction of the surrounding villi through its interference with the maternal circulation. It is possible for white infarcts to form without lesions in the arterial fetal system, but it is not at present known whether this is true of all infarcts.

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**Birth Control—Libel Action.**—A case is reported (*Jour. Am. Med. Assn.*, 1923, 80, 1016) occurring in London where a female physician, well educated and the president of a society and the author of several books on sexual subjects, brought action against a physician because he attacked her character in a book written by him on birth control. The plaintiff was conducting a clinic to teach contraceptive methods among the poor. On her side testimony was given to the effect that her books were decent and that her society and clinic were doing good. It was also testified that if cleanliness were maintained the

methods which she recommended were not dangerous. There was considerable testimony supporting the plaintiff. Testimony of equal value was given for the defendant. He was a Roman Catholic, but did not write the book at the suggestion of the Church. In summing up, the Lord Chief Justice submitted to the Jury four questions which were answered: Were the words complained of defamatory? Yes. Were they true in substance and in fact? Yes. Were they fair comment? No. What should the amount of damages be? \$500. After legal arguments the Judge gave judgment for the defendant.

**Separation of the Symphysis Pubis During Labor.**—TELFAIR recently reported before the New York Obstetrical Society (*Am. Jour. Obst.*, 1923, 5, 91) 3 cases of separation of the symphysis during labor. The first was a primipara, aged twenty-six years, who after a very long first stage was delivered by a high forceps application. During the extraction the pelvis was felt to suddenly give way. The baby was large, and there was profuse bleeding from the anterior vaginal wall. On examination, the entire anterior vaginal wall, urethra and labia were separated from the ramus pubi on the left side. The bladder was not injured and there was a separation of the pubic bones of about 3 cm. A retention catheter was inserted and lacerations repaired. Two days after labor a profuse, purulent discharge occurred from behind the pubes. The sacro-iliac joints were not involved. After a mild septic infection the patient made a tedious recovery. A fibrous union formed, and in four weeks the patient was able to walk without difficulty. In the second case a small multipara had a rapid, hard labor with large child. Delivery was spontaneous and followed by moderate shock. The roentgen-ray showed separation of the symphysis. There were no lacerations, and with retention dressings the patient made a good recovery, being able to walk on the sixteenth day without difficulty. The third case, a primipara, aged twenty-four years, was brought to the hospital still under ether, having just been delivered in her home by forceps and with the vagina packed to control hemorrhage. On the following day the packing was removed, but it was found that the anterior vaginal wall and urethra were torn from the pubic bones, the lacerations extending into the prevesical space. The pubic joint had been opened, and the ends of the bones were 10 cm. apart. A permanent catheter was used. The wound was packed to control hemorrhage and the pelvis strapped. On the day following there was a temperature of 103° F., pulse of 140, with pain and tenderness. For three weeks the patient was septic, but in five weeks had recovered and was able to walk. In discussion, a case was described in which a woman had premature twins, very easily delivered, but who also had a separation of the symphysis and a great deal of pain. In another case, during each of three pregnancies the patient suffered greatly from the symphysis and recovered as soon as pregnancy ended. Others reported quite as many of these cases after spontaneous as after instrumental delivery. The practice of applying the forceps to the floating head is thought to be the principal cause of this accident. In one such case the bladder was lacerated. One case was reported of postpartum separation of the symphysis. The woman was brought to the hos-

pital very septic from confinement outside the hospital, and on admission there was no separation of the symphysis. She developed an exudate outside the peritoneum, which ultimately opened into the labium. When the tissues were incised it was found that the patient's symphysis had lost its cartilage by the septic process. Ultimately she made a good recovery.

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## GYNECOLOGY

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UNDER THE CHARGE OF

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**Diagnosis of Cancer of the Uterus.**—It has been estimated that the prevalence of cancer of the uterus is increasing at the rate of about 2.5 per cent a year. The recent report of the Census Bureau contains the information that about 24 per cent of the deaths among women during the year were from cancer of the uterus. Cancer of the cervix is more common than cancer of the fundus, it is relatively more malignant and grows more rapidly. Surgery is supposed to offer the best chance of cure, yet less than 50 per cent of such patients come to the Mayo Clinic while the disease is in the operable stage, according to MELSON (*Minnesota Med.*, 1923, 6, 110). The operable cases in the series observed in the Mayo Clinic were 56 per cent in 1917, 45 per cent in 1918, 33 per cent in 1919, 23 per cent in 1920, and 24 per cent in 1921. In this series the primary symptoms in order of frequency were bloody discharge, watery leukorrhea, hemorrhage, intermenstrual spotting, profuse leukorrhea, frequent and prolonged menstrual periods, profuse menstrual periods, pelvic or low abdominal pain and bleeding after intercourse. Cancer of the fundus occurs so frequently after the menopause that the accompanying bloody discharge is often mistaken for a return of the menstrual flow. As the disease progresses the well-known symptoms of foul, watery discharge with frequent and often continuous severe bleeding and pelvic pain ensue. Unfortunately it is in this stage, when chance for permanent cure is usually passed that the greater number of patients come for examination, particularly in cancer of the cervix. The average duration of symptoms in these cases before the patient came to the clinic was eleven months. Unfortunately the duration of the symptoms and the extent of the disease do not always run parallel. In an early case from the standpoint of operability, the symptoms may be protracted, while in an advanced case the symptoms may have existed for a short time only, particularly in cancer of the infiltrating rather than the ulcerating type. Symptoms are mani-

fest in the incipient stage of cancer of the fundus and because the malignancy is confined to the uterus for a considerable period, operation may be advisable even if symptoms have been present for a comparatively long time. That the laity do not recognize the importance of the early symptoms of cancer is shown by the time interval between the onset of symptoms and the first consultation with the physician. In the cases of cancer of the cervix the average interval was seven months, while in cancer of the fundus the average interval was six and four-tenths months. If a diagnosis cannot be reached clinically in two or three days, material for microscopical examination should be obtained. If the examiner has satisfied himself that there is an indurated area, characteristically granular, and if there is a history of a vaginal discharge of unusual amount or character, Melson believes that a specimen of tissue should be removed by an experienced surgeon and examined by an experienced pathologist. The specimen should be taken and the examination made with the patient prepared for operation, so that, in case of malignancy, radical procedures may be carried out without delay. In cases with presumptive symptoms of cancer of the fundus, a diagnostic curettage should be performed and the tissue examined under like conditions. Melson would impress on us that any real advance in the treatment of uterine cancer must come through the medium of early diagnosis, since statistics show that in the early treated cases cure is the rule.

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**New Operation for Uterine Retroflexion.**—The operation which KEEFE (*Boston Med. and Surg. Jour.*, 1923, 188, 299) has added to the ever-increasing list of procedures for the radical cure of backward displacement of the uterus is performed in the following manner: The patient is placed in the Trendelenburg position at a greater angle than is usual. A modified Pfannenstiël, slightly curved, transverse incision is made through the skin and fat, down to the fascia covering the recti muscles. This incision, with its convexity toward the pubes, extends from a point one inch to the inner side of the anterior superior spine of the ilium to a like point on the opposite side, on a line with the upper border of the pubic hair. The flaps are dissected upward and downward for a distance of about five inches. A second vertical incision is made near the median line, at right angles to the original incision, through fascia, rectus muscle and peritoneum. A careful examination is now made of the abdominal contents and any pathological condition found is corrected. When the uterus is replaced in the normal anteverted position, the round ligaments are observed to be lax and of too great length to be of material assistance in holding the uterus in the new, yet normal position. The slack in the round ligaments is now taken up by shortening them with the following procedures: An incision two inches in length is made through the peritoneum covering the uterus and round ligament the center of the incision lying over the insertion of the round ligament into the uterus. The edges of the peritoneum along the incision are retracted and the uterine portion of the incision deepened sufficiently to receive the round ligament about to be imbedded in it. The round ligament, freed of its overlying peritoneal covering, is now grasped with forceps and drawn taut, in the

direction of the uterus, thus taking up the slack. The loop of round ligament resulting from this procedure is fixed in the slit in the wall of the uterus by three or four chromic gut sutures and the peritoneum is then drawn over the ligament and united with a continuous plain catgut suture. The opposite round ligament is treated in a similar manner. This part of the operation is then supplemented by a procedure which Keefe acquired from Pestalozzi, of Rome, consisting of making a transverse incision through the peritoneum one-half inch above the upper attachment of the bladder to the anterior uterine wall, separating the bladder from the uterus as far as the junction of the cervix with the vagina, pulling the bladder upward and attaching it with four interrupted chromic catgut sutures passed through the bladder musculature to the anterior wall of the uterus just below the insertion of the round ligaments. The bladder peritoneal flap is then sutured to the fundus of the uterus covering over the field of operation and the abdominal incision is closed.

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**Calculi in Upper Urinary Tract.**—Experience has taught MOORE (*Jour. Missouri State Med. Assn.*, 1923, 20, 113) to consider every calculus in the urinary system a menace and the earlier removed, consistent with the patient's convenience and general condition, the better. Stones within the kidney or pelvis 2 cm. or more in diameter, as a rule, never pass spontaneously, therefore operation is the rule. Whether nephrotomy, pyelotomy or nephrectomy is done depends upon the operator's judgment and choice after duly considering the facts at hand. Ureteral calculi offer an entirely different problem, due to the fact that a great number of them may be removed by manipulation with ureteral instruments through a cystoscope, while it is also true that many of them are expelled without any manipulation. Results obtained from the use of various intra-ureteral manipulations depend upon the location, size and shape of the stone. Many large smooth stones may be dislodged, where under the same technic smaller but irregular stones could only be removed by open operation. If the stone is not dislodged at the first ureteral catheterization, the author incises the ureteral orifice with a ureteral scissors so that a larger instrument may be passed upward or the stone may pass downward. A ureteral dilator is then passed up the ureter as far as the obstruction, if possible, and the ureter is dilated as the dilator is withdrawn. This may be repeated at intervals of four or five days. Injection through a ureteral catheter of a 2 per cent papaverine solution, to relax the ureteral musculature, and sterile olive oil, to lubricate the calculus and tract, have been used with good results. Similarly, surgical pituitrin injected subcutaneously at three-hour intervals for four or five doses is used for increasing ureteral peristalsis, and belladonna by mouth, to the point of physiological tolerance, is used for relaxation. Open operation for the removal of ureteral stones should be resorted to only after a sufficient length of time has elapsed and other means have failed, or when the obstruction is so complete that danger of kidney destruction is evident.

## PATHOLOGY AND BACTERIOLOGY

UNDER THE CHARGE OF

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**The Dominant Reacting Tissues in Anaphylactic, Peptone and Histamine Shock.**—"Canine anaphylactic shock, peptone shock and histamine shock are currently assumed to be identical physiological reactions. In each shock there is a sudden pronounced fall in arterial blood-pressure, the carotid pressure being reduced to about 25 mm of Hg by the end of two minutes. Recovery usually begins about the tenth minute, the arterial pressure being restored in from thirty to ninety minutes, depending upon the severity of the reaction. In each shock fatal results may be produced by the injection of large doses or by the use of highly sterilized animals. In each shock there is a pronounced splanchnic engorgement and cyanosis, the production of hemorrhagic lesions in the intestinal mucosa and a reduction of blood coagulability." In order to test the assumed physiological identity of the three shocks, MANWARING, CHILCOTE, CLARK and MONACO (*Proc. Soc. Exper. Biol. and Med.*, 1922, 20, 182) conducted a series of experiments on dogs in an endeavor to determine "the topographical distribution of the dominant reacting tissues in each shock." It was found that anaphylactic shock did not occur in dehepatized (Eck's fistula) dogs which were unduly or highly sensitized, there being practically no change in the arterial blood-pressure even after the injecting of as large a dose as 30 cc of horse serum. The severity of the peptone reaction was reduced in dehepatized dogs and was reduced, further, in completely eviscerated dogs. On the other hand, the severity of the histamine reaction was *not* reduced in dehepatized nor in eviscerated dogs, indicating that canine anaphylactic peptone and histamine shock are not physiologically identical reactions, at least as far as their initial or fundamental physiological mechanisms are concerned. The secondary reactions, which conceivably dominate the clinical picture in each type, are due to a low systemic blood-pressure and are presumably identical in the three shocks.

**The Hepatic Mechanical Factor in Canine Anaphylactic Shock.**—Certain observers have assumed that the sudden pronounced fall in arterial blood-pressure, the characteristic feature of acute anaphylactic shock in dogs, is due to the reduction of the available systemic blood volume as a result of splanchnic engorgement, which is a passive congestion due to hepatic obstruction. MANWARING, CHILCOTE and BRILL (*Proc. Soc. Exper. Biol. and Med.*, 1922, 20, 184) tested this theory by studying the effects on carotid blood-pressure of a mechanical obstruction to hepatic outflow sufficient to produce a combined hepatic and intestinal passive congestion equal to the passive con-

gestion observed in anaphylactic shock. Increase in portal blood-pressure was taken as the index of passive congestion. The inferior vena cava was ligated immediately below the liver in a series of dogs, and six weeks later a fully compensating collateral circulation was found to have been established. To make the tests an enclosed ligature was placed around the vena cava just below the diaphragm. By partially closing this ligature, any desired degree of hepatic passive congestion could be produced without interfering with the return circulation from the hindquarters. It was found that carefully controlled increased resistance to hepatic outflow, sufficient to raise the portal blood-pressure to 20 mm Hg, which is greater than the maximum portal pressure during anaphylactic shock, was without marked effect on the carotid blood-pressure. It was only when the vena caval ligature was completely closed so as to produce combined hepatic and intestinal stasis that a fall in carotid pressure was produced, at all comparable with the fall produced during anaphylactic shock. The authors conclude from these tests that the hepatic-intestinal passive congestion, though conceivably a factor of some importance to canine anaphylactic shock, is not the essential or dominant factor in this shock, thereby strengthening their original theory that the anaphylactic reaction in dogs is essentially an explosive hepatic auto-intoxication, the formation or liberation of hepatic products having a histamine-like action on the extrahepatic bloodvessels.

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**Clinical Results Outlined with *Bacillus Acidophilus*.**—By giving a daily dose of 1000 cc containing 200,000,000 viable *Bacillus acidophilus* per 1 cc to a series of 30 constipated subjects, KOPELOFF (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 424) found that the number of normal defecations was considerably increased during the treatment and that the beneficial influence of *Bacillus acidophilus* persisted for a considerable period of time after treatment had been discontinued. The use of lactose during and after ingestion of *Bacillus acidophilus* enhances the beneficial effects. A transformation of the intestinal flora from a proteolytic to an aciduric type, as shown by microscopical and plate counts, was usually accompanied by almost daily defecations regardless of the severity of the constipation. Two cases of diarrhea were treated successfully by the ingestion of *Bacillus acidophilus*.

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**The Occurrence of Intranuclear Inclusion Bodies in Certain Tissues of the Rabbit Inoculated Directly with the Virus of Herpes Labialis.**—GOODPASTURE and TEAGUE (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 400) were able to demonstrate characteristic intranuclear bodies like those described by Lipschutz, by inoculating a virus obtained from a herpetic vesicle from the human lip upon the scarified cornea of a rabbit. Purulent secretion was collected twenty-four hours after inoculation of cornea, suspended in saline solution and injected in small quantities with a hypodermic syringe into various tissues of rabbits. The intranuclear bodies were encountered in the cornea, in the nerve and glial cells of brain, in the ciliated epithelium of trachea, in the cortical cells of adrenal, in the parenchymatous cells of liver, in the cells of Leydig of testes and in the squamous epithelial cells of skin. Only within cells within the lesion could these bodies be demonstrated. Herpetic virus was shown to be present in the inoculated

brain, testicle and adrenal after inoculation of the rabbit's cornea. The authors believe that the demonstration of these round or oval, acidophilic or homogeneous or faintly granular bodies "within the nuclei of cells in the inoculated area is diagnostic of a take indicating proliferation of the virus of herpes labialis locally."

**The Transmission of the Tetanus Antitoxin Through the Placenta.**—Having shown that when tetanus bacilli are present in the stools of man an appreciable amount of antitoxin can be found in the blood, and having used this fact to explain in part the relatively low incidence of tetanus infections in Peking, where about a third of the population are carriers of *Bacillus tetani*, TEN BROECK and BAUER (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 399) conducted several examinations to determine whether or not the antitoxin passes the placenta. The stools of 14 of the mothers examined failed to show tetanus bacilli and none of their sera were able to neutralize 2 M. L. D. of toxin. Tests on the sera of their children were likewise negative. Six of the mothers proved to be carriers of tetanus bacilli, and, with one exception, when tetanus antitoxin was found in the mother's serum it was also present in the cord blood, and in the majority of cases the level in the two bloods was approximately the same, suggesting that the placenta is permeable to this antibody which would appear to have a simpler structure than the other so-called immune bodies which fail to pass this organ. Two of the babies were born with approximately 0.25 units, 1 with 0.1 unit, 2 with 0.05 unit and 1 with no appreciable tetanus antitoxin in 1 cc of serum.

**The Specific Soluble Substance of Pneumococcus.**—“In 1917 Dochez and Avery showed that there was contained in filtrates from a pneumococcus culture and in the body fluids of experimentally infected animals and patients suffering from pneumonia, a soluble substance which reacts specifically in antipneumococcic serum of the homologous type. This substance which was found to be thermostable, precipitable by acetone or alcohol, non-dialyzable, and not digested by trypsin,” has been subjected to a more intensive chemical study by HEIDELBERGER and AVERY (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 434) whose findings are given *verbatim*: “Eight-day, autolyzed cultures of Type II pneumococcus in phosphate broth were concentrated to  $\frac{1}{3}$  volume and precipitated with 1.2 volumes of alcohol. The precipitate, centrifuged at high speed, yields a compact middle layer containing the specific soluble substance. By repeated fractionation with alcohol or acetone, first in neutral, then in acetic acid solution, followed by repeated fractional precipitation with ammonium sulphate and final dialysis, about 1 gm of a highly purified preparation was obtained for each 75 liters of culture used. In its present state of purity the specific soluble substance is amorphous and yields a viscous solution in water. A 1 per cent solution gives no biuret test, yields no precipitate with phosphotungstic acid, mercuric chloride, or lead acetate, gives a faint haze with tannic acid, and is precipitated by basic lead acetate. At a dilution of 1:1,500,000 it still gives the Molisch reaction and yields a precipitate with Type II serum: D is plus 58.7; N, 1.2 per cent; P, trace; S, none; C, 46.2 per cent; H, 6.1 per cent. Hydrolysis yielded 79 per cent of reducing



sugars, of which glucose was identified by the melting-point and optical rotation of its phenylosazone. Earlier preparations containing more nitrogen and yielding less reducing sugars on hydrolysis were not specific as high dilutions. While it is not excluded that the non-carbohydrate portion of the preparation is actually the carrier of the specific reaction, it is believed that the evidence points to the identity of the specific soluble substance with the polysaccharide portion, thus linking it with the bacterial gums isolated by others from capsular material, but never before connected with specificity."

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## HYGIENE AND PUBLIC HEALTH

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**Botulism and the Bacillus Botulinus.**—The bacteriology of botulism has up to the present time received scanty attention, because the investigation of the subject is fraught with technical difficulties and because the physiological or experimental study of the disease itself offers more dramatic and obvious results. According to Burke, of Stanford University, only twelve pure cultures of *Bacillus botulinus* were available in 1919 in the United States, while in 1921, Weiss, in his studies at Harvard, was able to use sixteen toxin-producing strains. *Bacillus botulinus* had been cultivated in relatively few instances from the occurrences of botulism in Europe, namely, twelve isolations have been accomplished. The work of Meyer and his colleagues, of the University of California, and of Thom and his associates, of the government laboratories in Washington, and other American workers has demonstrated recently that this anaërobe can be readily detected and purified from spoiled food material, provided suitable procedures and specimens are examined. Thirty-five of the 101 recorded outbreaks in America have been proved bacteriologically or toxicologically. DUBOVSKY, MEYER and others (*Jour. Infect. Dis.*, 1922, 31, 6, 501) advance our knowledge of *Bacillus botulinus* considerably. DUBOVSKY and MEYER (Study No. I) describe the methods employed for the enrichment and demonstration of *Bacillus botulinus* in specimens of soil and its products. The composition of the medium, the preparation and heating of the samples, the period of incubation and storage, the identification of the toxin and the isolation of the organism from toxic enrichment cultures are discussed and their value considered in the light of numerous experiments. It is emphasized that inexperienced workers should question their results until they eliminate the danger of laboratory contamination by continuous, painstaking vigilance, proper sterilization of the culture mediums, glassware, etc., and

by repeated control examination. The methods applicable for the examination of suspected food, clinical and necropsy material, are described in detail. MEYER and DUBOVSKY (Ibid., Study No. II) state that the evidence strongly suggests that the natural habitat of *Bacillus botulinus* is found in virgin mountain or forest soil. *Bacillus botulinus* is also present in cultivated garden and field soils and their products. Vegetables and fruits bought in various cities and towns of California carry the spores of *Bacillus botulinus*. Type B occurs predominantly in cultivated and manured soils, and is probably a mutant of the fixed Type A. COLEMAN (Ibid., Study No. III) found that the cultivated soils of a narrow strip of coast line in Santa Barbara County, California, are heavily contaminated with the spores of *Bacillus botulinus*, Type A, as well as with those of *Bacillus tetani*, and that the virgin soil from the mountain range behind this strip of land contains the spores of *Bacillus botulinus*, Type A. MEYER and DUBOVSKY (Ibid., Study No. IV) studied the distribution of the spores of *Bacillus botulinus* in the United States. They made a general survey, during which 1538 soil, vegetable, feed and manure specimens of every state of the United States except Virginia were studied. They state that *Bacillus botulinus* is a common soil anaërobe of the western states of the Cordilleran system. It is less frequently encountered in the Atlantic states and is relatively rare in the middle states, the Great Plains and the Mississippi Valley. The soil of the western states, inclusive of the Great Plains, yield, mainly, *Bacillus botulinus*, Type A, while the Mississippi Valley and the Great Lakes Region is characterized by a striking predominance of Type B. Similarly prevalent is this latter type in the Atlantic states of Maryland, Delaware, New Jersey, Georgia and South Carolina, while scattered findings of Type A in Maine, New York and Pennsylvania indicate the existence of breeding places in virgin forests and mountains. Soils which are subjected to intensive cultivation and fertilization contain, as a rule, *Bacillus botulinus*, Type B. *Botulinus* spores are far more prevalent in virgin and pasture soils than in dirt, soil or manure collected from animal corrals, pig-pens, etc. Vegetables, fruits and feeds are frequently contaminated with the spores of *Bacillus botulinus*. String-bean pods and leaves, moldy hay, ensilage and decayed vegetation may yield a relatively high percentage of positive cultures. Human and animal botulism is not infrequent in those states in which *Bacillus botulinus*, Type A, predominates, or in which the percentage figures of positive cultures exceeds 20 to 30 per cent. From a practical standpoint, however, *Bacillus botulinus* is ubiquitous, and this survey gives no assurance that heat resistant spores cannot be found anywhere and at any time. The theory which claims that all the pathogenic anaërobes are regular inhabitants of the intestinal canal of animals deserves renewed investigation in the light of this survey on *Bacillus botulinus*. DUBOVSKY and MEYER (Ibid., Study No. V) studied the distribution of the spores of *Bacillus botulinus* in Alaska and Canada. They could not demonstrate *Bacillus botulinus* in the coast land soil of the Aleutian Archipelago. *Bacillus botulinus*, Type A, and occasionally Type B, was cultivated in moraine, glacier and mountain soil collected around Lake Louise in the Canadian Rockies. Soil samples obtained from the provinces of Prince Edward Island, Nova Scotia, Quebec, Ontario and British Columbia also furnished positive cultures. These

same investigators (Ibid., Study VI) studied the occurrence of the spores of *Bacillus botulinus* in Belgium, Denmark, England, the Netherlands and Switzerland, and demonstrated Type B in soil and vegetable specimens collected in each of these countries. *Bacillus botulinus*, Type A, was found consistently absent. The spores are widely distributed, but they are neither numerous nor very resistant to heat. SCHOENHOLZ and MEYER (Ibid., Study No. VII) state that *Bacillus botulinus*, Type B, is frequently found in the soils obtained from the Island of Oahu, in the Territory of Hawaii, and from the provinces of Chilili and Shansi in China. Type A has been found only in two Hawaiian and in one Chinese soil specimens. COLEMAN and MEYER (Ibid., Study No. X) confirmed the work of ORR with reference to the pathogenicity of toxin-free spores of *Bacillus botulinus*. They conclude that massive doses of toxin-free spores of *Bacillus botulinus* are pathogenic when introduced into the animal body. These spores and the vegetative forms arising from them are rapidly disseminated throughout the tissues of the body. Toxin-free spores of *Bacillus botulinus* germinate and the vegetative forms arising from this germination multiply and liberate toxin in the animal body. ESTY and MEYER (Ibid., Study No. XI) studied the heat resistance of spores of *Bacillus botulinus* and allied anaërobes with the following results: The heat resistance of 109 strains of *Bacillus botulinus* (78 Type A, 30 Type B and 1 non-toxic) from various sources varied from three to eighty minutes at 105° C. The maximum heat resistance of *Bacillus botulinus* spores artificially produced under the most favorable conditions for growth and heated in a phosphate solution of a PH 7.0 was as follows: Four minutes at 120° C.; ten minutes at 115° C.; thirty-two minutes at 110° C.; one hundred minutes at 105° C.; three hundred and thirty minutes at 100° C. These results represent actual survival times at the given temperatures. The heat resistance of spores of the same strain of *Bacillus botulinus* varied considerably, depending upon several factors, some of which are unknown. The average resistance of the spores of *Bacillus botulinus*, as found in approximately 20 gm, either of naturally or artificially contaminated soil, was less than three hours at 100° C. The death-rate of *Bacillus botulinus* spores was gradual and followed in a general way the laws of logarithmic decline. The majority of the spores were not exceptionally heat-resistant. Young moist spores, probably those of the first generation, appeared to be the most heat-resistant.

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ORIGINAL ARTICLES.

THE PHYSICAL FINDINGS IN PERICARDITIS WITH EFFUSION.<sup>1</sup>

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THE diagnosis of a pericardial effusion is often a matter of great difficulty. Even with the most painstaking physical examination, a large effusion may be missed, as all clinicians who follow their patients to the autopsy table realize. This fact indicates that the physical signs of pericardial effusion are not always distinctive, and led one of the writers (R. S. M.) and Bader<sup>2</sup> to study the problem experimentally.

In these experiments, ascitic fluid was injected into the pericardium of fresh cadavers within four hours after death. Particular attention was paid to the shape of the cardio-hepatic angle and to the shape and extent of the relative cardiac dulness and the cardiac shadow in radiograms. It was found that the cardio-hepatic angle is acute—at the most a right angle, but never obtuse in the injected pericardia—even after the introduction of 2 liters of fluid. The

<sup>1</sup> Presented at the meeting of the Association of American Physicians at Atlantic City, N. J., May 1, 1923.

<sup>2</sup> A Comparison of the Percussion and Roentgen-ray Findings after Injection of the Pericardium, Jour. Am. Med. Assn., 1917, 69, 450.

least amount of fluid causing a change in the percussion findings was 250 cc (inconstant), but it was not until 500 cc had been injected that definite percussion and roentgen-ray changes could be detected with uniformity. It was further observed in the experimental injections that there is a marked widening of the retromanubrial dulness at the base of the heart, with a corresponding increase in width of the shadow in the radiograms, and, what is probably of greater practical importance, that the area of dulness and the extent of the shadow in this region decrease in width when the cadaver is changed from the recumbent to the erect posture.

The present report is the result of a continuation of the earlier work, but instead of cadavers, we have confined our observations to patients ill with pericarditis.

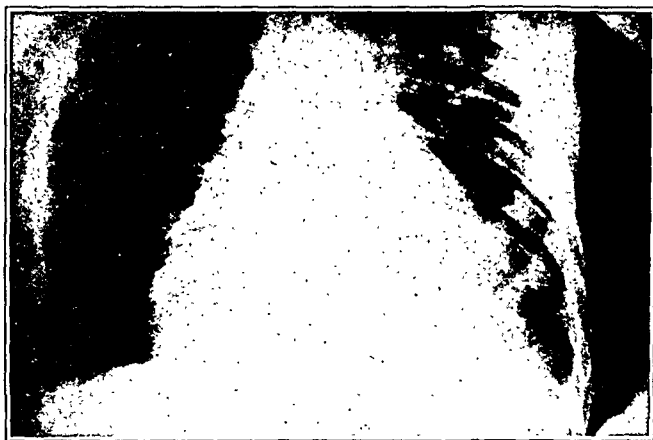


FIG. 1.—Teleroentgenogram pericarditis with effusion.

Our attention has been focussed again chiefly on the percussion findings, though we, like others, have been impressed with the fact that even with large accumulations of fluid in the pericardium, the apex impulse *may* remain visible and palpable and the heart sounds of good intensity throughout the course of the disease; and that, at times, a pericardial friction rub may persist along the left sternal border, near the base of the heart.

In many of the text-books on diagnosis, the statement is made that the cardio-hepatic angle becomes obtuse as fluid accumulates in the pericardium. In the past two and a half years, we have found the angle to be acute, both by percussion and by roentgenologic examination (teleroentgenograms and fluoroscopy) except in a few instances in which a right angle was determined (Figs. 1, 2, 3). In no instance was the angle obtuse. The percussion was carried out with the eyes averted or closed; direct percussion, using the second finger, was employed. The shape of the angle has been practically

unaffected by changing the patient from the recumbent to the erect posture.

The shape of the area of relative cardiac dulness is a matter of considerable interest. It is pear-shaped, except when pericardial adhesions or extra-pericardial lesions interfere with the distention of the sac by the fluid. There is an early increase of the cardiac dulness both to the right, in the third and fourth interspaces, and to the left, beyond the apex. This is more marked when the patient assumes the erect posture, and there is a corresponding change in the fluoroscopic shadow.

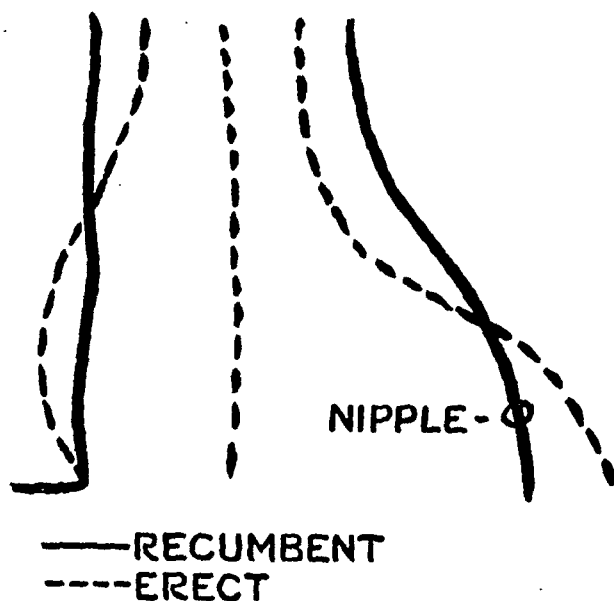


FIG. 2.—Pericarditis with effusion. Relative cardiac dulness in the recumbent (continuous line) and erect (broken line) postures.

Of greater practical importance, in our experience, has been an extension of the relative dulness upward in the first and second interspaces. In this connection, the fact may be recalled that the pericardium extends along the great vessels for a distance of  $1\frac{1}{2}$  to 2 inches from their point of origin in the heart; the entire ascending aorta is within the pericardium. An early filling of these cul-de-sacs, as evidenced by an increase in the width of the area of dulness and of the shadow when the patient is recumbent, is one of the most important physical signs of a pericardial effusion. If the dull area and shadow become narrower when the patient is erect, it is indicative of fluid. Thus far, we have encountered this physical sign only in connection with pericardial effusion and have not failed to demonstrate fluid when shifting retromanubrial dulness was found (Fig. 2). Thus, our clinical studies confirm the results obtained experimentally.

The absence of visible pulsation has been noted fluoroscopically repeatedly with large effusions, and has been an aid in the differentiation of this condition and cardiac dilatation. With smaller effusions, a slight pulsation may be observed.

Dulness in the left back near the angle of the scapula, with bronchial breathing, pectoriloquy and bronchophony or egophony, at times with diminished breath sounds and decreased tactile fremitus, noted by many observers, has proved a helpful sign with large effu-

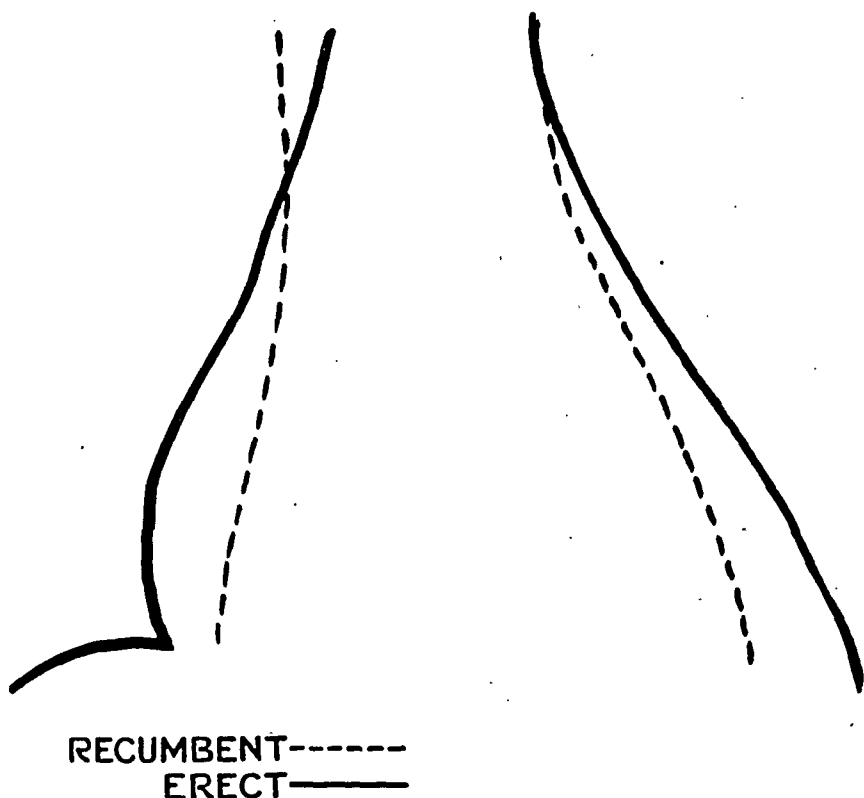


FIG. 3.—Pericarditis with effusion. Fluoroscopic tracing of the cardiac shadow in the recumbent (broken line) and erect (continuous line) postures. (Note. The findings recorded in Figs. 2 and 3 are not from the same patient.)

sions. In one instance, the extent of the dull area was so great that a pleural effusion was diagnosed, but aspiration and subsequent study made it altogether probable that the pericardium had been aspirated.

**Conclusions.** 1. The cardio-hepatic angle in pericardial effusion is usually an acute angle.

2. The area of relative cardiac dulness in effusion is pyriform and generally extends upward to the first interspace.

3. Widening of the area of dulness and of the shadow in the first

and second interspaces occurs relatively early in effusion and is best determined with the patient in the recumbent posture.

4. Shifting dullness (*i.e.*, a narrowing of the dull area, with a corresponding decrease in width of the shadow over the great vessels when the patient is changed from the recumbent to the erect posture) has proved to be the most reliable physical sign of fluid in the pericardium.

5. Widening of the dull area and of the shadow to right and left above the diaphragm when the patient is erect is found with fluid.

6. There is an absence or marked decrease of visible pulsation in the shadow fluoroscopically in pericardial effusion.

7. Dulness at the angle of the left scapula is often present with a large accumulation of fluid in the pericardium.

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## STRUCTURAL AND FUNCTIONAL INVOLVEMENT OF THE HEART FOLLOWING ACUTE RESPIRATORY AND OTHER ACUTE INFECTIONS.\*

(SECOND PAPER.)

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THREE years ago, before the 1920 meeting of the Association of American Physicians, one of us (W. W. H.) presented 6 cases of involvement of the auricle and conduction pathways of the heart following influenza.<sup>1</sup> In this report, it was stated that epidemic influenza causes damage to the cardiac mechanism which may be demonstrated clinically and electrocardiographically, and that this type of infection singles out, to a degree exclusively, the auricle and conduction pathways. The results of these infections were shown to be chronic cases of cardiac involvement, showing arrhythmia and involvement of the auricle, persisting and causing partial invalidism long after the subsidence of the acute infection, lasting from twelve to seventeen months and longer. It occurred to us that it might be desirable to reconsider these 6 cases at this time, to determine if possible the end-results of these acute influenzal infections

\* Read at the thirty-eighth meeting of the Association of American Physicians, Atlantic City, May 1, 1923.

<sup>1</sup> Hamburger, W. W.: Involvement of the Auricle and Conduction Pathways of the Heart following Influenza, *AM. JOUR. MED. SCI.*, 1920, 160, 479.



as to the permanency or lack of permanency of such heart involvement. We have attempted to do this and shall make the first part of this report a brief summary of these cases, with the addition of 2 cases which were observed at that time but were not reported. The second part will consist of an analysis of 8 additional cases of involvement of the heart following acute respiratory and other acute infections observed during the past nine months, for the purpose of throwing additional light on this type of cardiac involvement and, if possible, to broaden and crystallize our views on this subject.

Since our original article, one or two noteworthy contributions to this subject have appeared. Paul White,<sup>2</sup> in a general discussion of the heart in infectious disease, considers the effects of influenzal infections to be transient and speaks of them as temporary poisoning. He believes that many symptoms, such as dyspnea, palpitation and precordial pain, are more likely evidence of effort syndrome or irritable heart than of actual structural cardiac involvement. Likewise, Hamilton and Lahey,<sup>3</sup> in an attempt to differentiate hyperthyroidism and heart disease from neurasthenic states, feel that such complaints as breathlessness, tachycardia, heart pain, vasomotor disturbances, etc., are all common to neurasthenia, heart disease and hyperthyroidism. Breathlessness, tachycardia, cyanosis and heart pain do not alone justify the diagnosis of heart disease, as they are found in a variety of conditions, convalescence, fear, fatigue, etc., when the heart is perfectly sound. They emphasize also that neurasthenic states may and frequently do complicate other organic disorders, and that the acute heart disease patient may be disabled by neurasthenic symptoms, complicating, but in no sense directly due to, pathological conditions of the heart. Romberg,<sup>4</sup> in discussing the cardiac findings following influenza, states that acute myocarditis should not be attributed to this condition, and quotes Fahr, who found myocarditis only once among 246 influenza postmortems, although 30 of these cases showed a marked dilatation of the heart. Romberg believes that epidemic influenza produces a functional involvement of the heart muscle, the result of toxic influences, while later certain cardiac symptoms appear, the result of widespread involvement of the entire organism from the infection. He has observed during the epidemic, striking symptoms of arrhythmia, extrasystoles, conduction disturbances, dilatation and muscular mitral insufficiency; during convalescence, evidences of heart weakness, angina-like attacks, here and there arrhythmias or marked bradycardias. The duration of the heart involvement, he found, ranged from a few days or weeks to several years, and mentions one patient,

<sup>2</sup> AM. JOUR. MED. SCI., 1922, 163, 335.

<sup>3</sup> Jour. Am. Med. Assn., 1922, 78, 1793.

<sup>4</sup> Lehrbuch der Krankheiten des Herzens, 1921, p. 493.

a man, obese, a heavy wine-drinker, nervous, who experienced shortly after an influenzal attack his first heart involvement and died within eighteen months of heart muscle insufficiency. His markedly dilated heart showed, even with the most careful microscopical study, no other demonstrable pathological changes, no evidence of coronary sclerosis, myocarditis, fatty degeneration of the muscle fibers or other changes in the musculature.

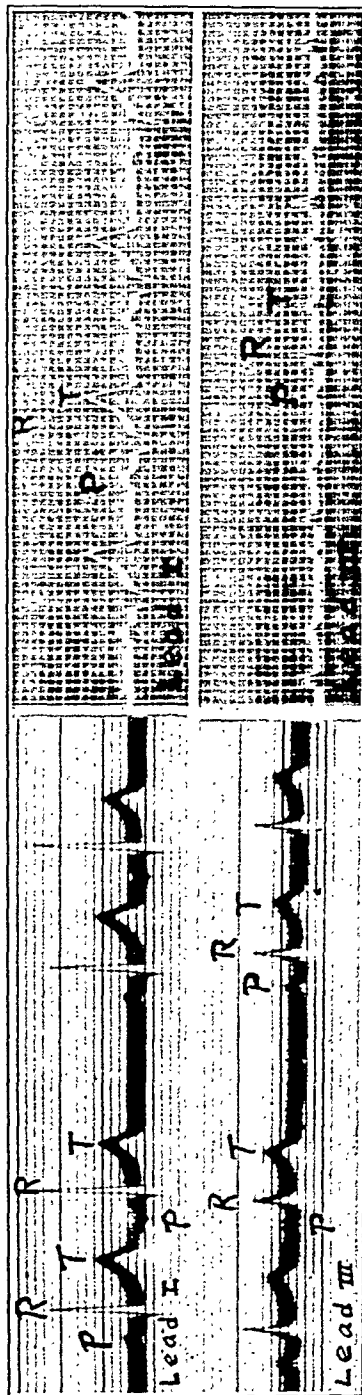
TABLE I.—CASES REPORTED 1920–1921. SUBSEQUENT REPORT.

Case.	Diagnosis (1920).	Present status (1923).
1 S. R.	Postinfluenzal auricular myocarditis,† Pulsus bigeminus. Auricular extrasystoles.	Marked improvement. Only occasionally shortness of breath. Complete disappearance of extrasystoles and bigeminus.
2 Dr. S.	Postinfluenzal myocardial insufficiency.	Not heard from.
3 C. H. W.	Postinfluenzal right ventricular extrasystoles. Ectopic auricular contractions.	No complaints. Occasional extrasystole. EKG shows inverted P <sub>2</sub> and right ventricular extrasystoles.
4 Dr. B.	Acute streptococcus myocarditis,† with auricular extrasystoles and partial A-V block.	Entirely recovered. "No heart lesion that can be detected."
5 Miss E. S.	Acute streptococcus myocarditis,† with partial 3-2 A-V block.	Not heard from.
6 Miss H. N.	Chronic postinfluenzal myocarditis,† with auricular extrasystoles.	Only slight improvement. Frequent attacks of "grippe." Tires easily. Auricular and ventricular extrasystoles.
7 J. M.	Acute postinfectious (streptococcus) myocarditis.† Acute, complete A-V and right bundle branch block.	Entirely recovered. EKG normal.
8 J. C.	Post-infectious (streptococcus, diphtheria) myocarditis,† and nephritis.	Entirely recovered. EKG normal.

† Not based on histological examination.

**Cases Reported in 1920.** Of the 8 cases reported in 1920, we have been able to trace 6. The first one, a teamster, aged twenty-five years, who, following a severe attack of influenza in April, 1919 was completely incapacitated from his occupation, was listed in our earlier report as a postinfluenzal auricular myocarditis, pulsus bigeminus, auricular extrasystoles. In April, 1920, a year after his influenza infection, this patient was able to take care of a small newsstand to which occupation he was obliged to change, because of his inability to work as a teamster. Examination in April, 1923, four years after his influenza, shows him markedly improved and apparently free from symptoms except occasional shortness of breath on severe effort. Evidences of dilatation of the heart have entirely disappeared, his heart borders being within normal limits. There is no evidence of auricular extrasystoles or bigeminal pulse, which three years ago were brought out, particularly upon exercise. Fig. 1 shows a comparison of his electrocardiographic curves in 1920 and 1923, showing the complete disappearance of the auricular involvement.

This case then should be put down as a complete recovery from a rather widespread involvement of the auricle following influenza within a four-year period.



Series I.

Series VI.

FIG. 1.—Case No. I. S. R. (teamster), post-influenzal auricular myocarditis. Series I, pulsus bigeminus, auricular extrasystoles (taken in 1920 during acute infection). Series VI, normal cardiac mechanism, showing absence of extrasystoles and bigeminus (taken April, 1923).

CASE II.—Physician from the South; we have been unable to locate.

CASE III.—Merchant, aged fifty years, with influenza in September, 1918, and recurrence in November, 1918, was diagnosed as a postinfluenzal auricular and ventricular involvement, with right ventricular extrasystoles and ectopic auricular contractions. Examination in February, 1923, four and a half years after his influenza, shows no symptoms or complaints of any description, no dyspnea; an occasional extrasystole still present. Fig. 2 shows his present electrocardiographic curves.

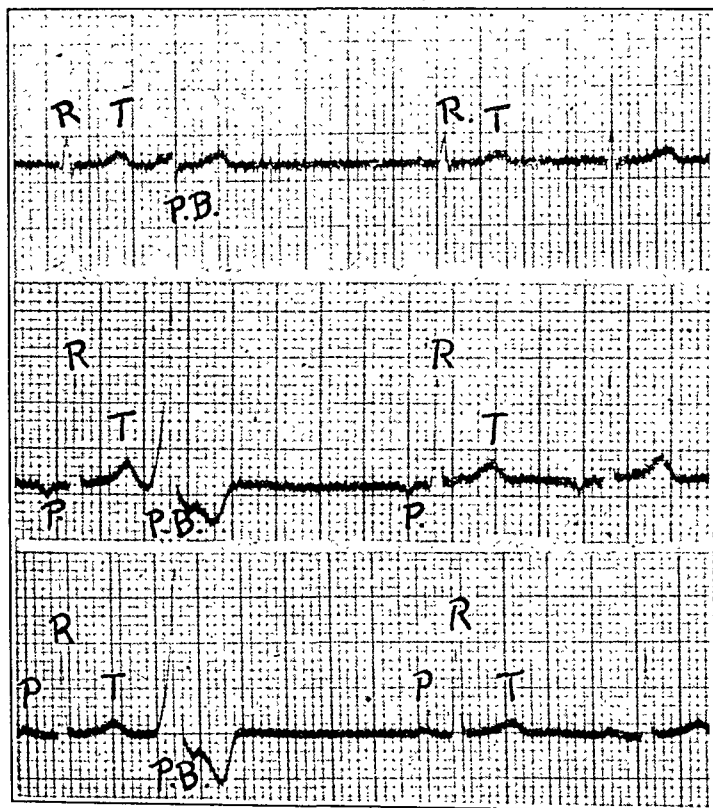


FIG. 2.—Case No. III. C. H. W. (merchant), right ventricular extrasystoles, inversion of  $P_2$  probably indicative of abnormality in the origin and path of the excitation wave in the auricle, inversion of  $P_3$  present in curves three years ago not present now.

CASE IV.—Physician, aged twenty-eight years, who was diagnosed in 1920 as acute streptococcic myocarditis involving particularly the auricle and conduction pathways, reports by letter, March 25, 1923: "I have never felt better in my life. Since leaving the hospital I have refereed football games, have danced and taken more exercise than I have in a number of years, all without discomfort. I have no heart lesion that can be detected. My blood-pressure is 135/80. I am still overweight, but I have

lost 25 pounds since I have been here. I have been able to take out life insurance, being rated up a little on account of my weight. Otherwise I am O.K."

CASE V.—A pupil nurse. This patient, we were unable to locate.

CASE VI.—Stenographer, aged twenty-eight years, who believed her heart trouble followed influenza in October, 1918, and who was diagnosed as chronic postinfluenzal myocarditis with localization in the auricle resulting in auricular extrasystoles has not made as satisfactory a recovery as the others. She has had repeated attacks of "grippe," becomes exhausted easily, has had transitory attacks of vertigo, with numbness of extremities and occasional precordial soreness. Examination at the present time shows a rapid pulse, irregular in rhythm and force; right heart border, 3.5; and left, 10.5 cm., from the midsternal line; slight uncleanness of the first tone of the apex which becomes more noticeable on sitting up; 10 to 12 extrasystoles per minute. The electrocardiogram at present, shows, in addition to the original auricular involvement, extrasystoles arising also from the ventricle. One must conclude that this patient still shows evidence of both auricular and ventricular involvement and should continue under observation to determine, if possible, the final outcome of the heart findings.

CASE VII.—This patient, a boy, aged thirteen years, was not included in the original 6 cases, but was published a few months later in the Chicago number of the *Medical Clinics of North America*.<sup>5</sup>

This boy, following an acute follicular tonsillitis, from which pure cultures of hemolytic streptococcus were isolated, developed on the sixth or seventh night of his illness, shortly after midnight, a sudden and complete auriculo-ventricular heart-block with a radial pulse of 28 beats per minute (Fig. 3). At the time, this boy was diagnosed as an acute postinfluenzal (streptococcus) myocarditis, involving particularly the bundle of His and its branches and resulting in transitory complete auriculo-ventricular dissociation and right bundle branch-block. Two weeks after the onset, however, electrocardiograms showed a practically normal cardiac mechanism and a week later he left the hospital apparently entirely recovered. At the present time he is free from complaints of any description and is attending school, preparing himself for a professional career. Physical and electrocardiographic examination are negative.

CASE VIII.—The eighth case, which occurred at about the same time as the others but reported now for the first time, concerns

<sup>5</sup> Hamburger, W. W.: *The Administration of Digitalis in the Presence of Certain Acute Infections*, *Medical Clinics of North America*, July, 1921, p. 101.

itself with a young man, aged thirty years, a salesman, who, following an acute streptococcus and diphtheritic sore throat early in 1921, developed weakness, dyspnea on exertion, bradycardia, palpitation and pain. Examination showed a moderate dilatation of his heart, the left heart border being 1 to 1.2 cm. outside of the left nipple. The other findings were negative, except those traceable to a subacute glomerular nephritis, *i. e.*, albumin, granular casts and a blood-pressure of 140/90, slight diminution of his thalein output and increase in the non-protein nitrogen of the blood. Examination on March 19, 1923, shows a slight increase in the degree of left ventricular preponderance, as compared with his findings two years before.

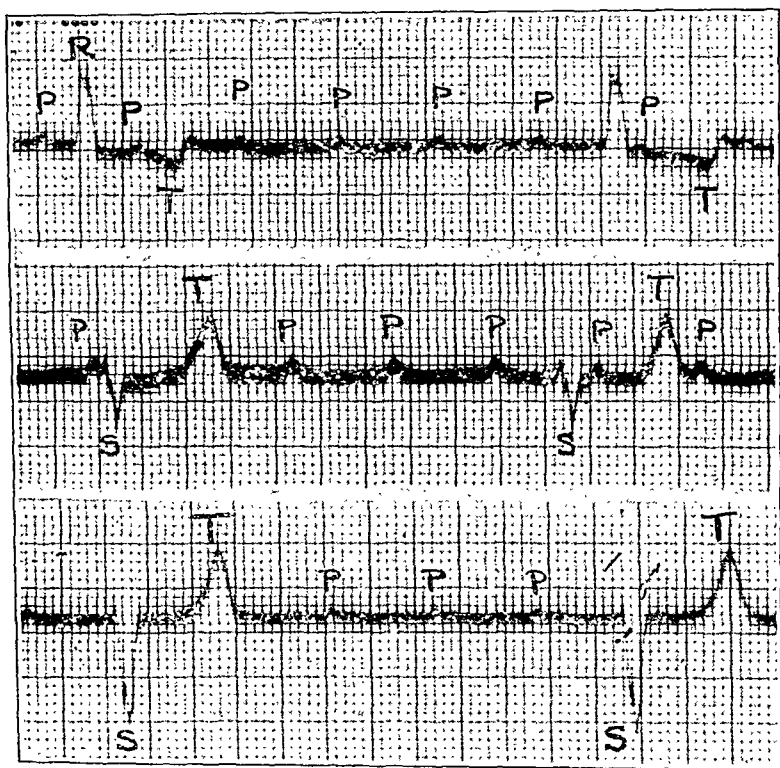


FIG. 3.—Case No. VII. J. M., school boy, aged thirteen years, acute infectious (streptococcus) myocarditis with complete A-V and right bundle branch block. Leads I, II, III taken October 27, 1920, on entering hospital. First published Medical Clinics North America, July, 1921.

Summarizing the results of these 8 cases, 5 patients present no complaints, particularly no cardiac complaints, and have apparently entirely recovered from the effects of their influenzal involvement. One patient still shows evidence of auricular and ventricular disease and 2 patients cannot be traced. One must conclude, therefore, with White, Romberg and others, at least so far as this small series is concerned, that the effects of influenza are

transitory in character, that, although widespread involvement of the heart may be demonstrated at the time of or shortly following the acute infection, within a four-year period these effects have completely disappeared. From the findings of these cases, it is extremely difficult, however, to conclude finally as to the exact nature of the involvement following influenza in terms of pathological anatomy and pathological physiology. One is not quite satisfied with the statement of an acute poisoning, but without experimental or histological findings it is impossible to say whether the effects observed might be due to cloudy swelling, edema, acute myocarditis, acute neuritis of the vagus or other pathological involvement. In this connection, White speaks of a transient heart-block occurring in rheumatic fever in hearts which do not show signs of pathological changes or pericarditis. He concludes that the occasional finding of acute heart-block should make one feel that any person who has suffered from rheumatic fever is not likely to have a perfectly normal heart, even though it appears normal to auscultation and percussion. Cowan, Fleming and Kennedy<sup>6</sup> found, on sectioning the auriculo-ventricular node and bundle of a girl, aged ten years, dying of diphtheria with complete heart-block, an acute inflammatory process, with separation and diffuse interstitial inflammation of the muscle fibers. In a male, aged twenty-six years, with heart failure following a cold and death from cerebral embolism, section of the heart showed marked congestion of the auriculo-ventricular node, with small foci of round cells in the bundle and early interstitial myocarditis.

Magnus Alsleben<sup>7</sup> found in 4 cases of heart-block (studied microscopically) that a transient partial heart-block is of frequent occurrence during the course and convalescence of acute infectious disease, and concludes that there is probably no lesion of the bundle itself, the block being vagal in origin.

Gerhardt<sup>8</sup> reports the case of man dying from typhoid fever, who previously had a transitory heart-block following rheumatism. Examination showed a definite lesion of the bundle, consisting chiefly of cellular infiltration chiefly in the region of the vessels.

Allen<sup>9</sup> believes, and quotes Lewis in support, that all transitory blocks are on the basis of organic lesions of the bundle, rather than on vagus effects, and concludes that such evidence of involvement of the bundle by partial or transitory block is certain evidence of myocardial change.

As we stated in the 1920 report, we have had no opportunity for microscopical study of hearts following influenza and showing clinical and electrocardiographic evidence of involvement of the

<sup>6</sup> Heart Block and Nodal Rhythm in Acute Infections, *Lancet*, 1912, 1, 277.

<sup>7</sup> *Ztschr. f. klin. Med.*, 1910, 69, 82.

<sup>8</sup> *Deutsch. Arch. f. klin. Med.*, 1912, 106, 462.

<sup>9</sup> *British Med. Jour.*, 1913, 1, 484.

conduction pathways, so that direct proof of this point cannot be offered in this series of cases. However, from our experience and a study of the literature, we incline to the view that partial or complete block is due to organic changes in the bundle rather than to vagal influences, although conceivably both might be present. The fact that these changes may be transitory does not itself speak against this view.

Also, our experience, that the majority of these cases cleared up within a three- or four-year period, does not speak against this conclusion. Either the scarring of the bundle, the theoretical result of such involvement, could be of such degree which would not affect the conduction pathways, or the cloudy swelling, edema, hemorrhage, cellular infiltration and acute interstitial inflammation which formed the structural basis of the detected temporary functional defect might be entirely recovered from. Whether or not involvement at one time predisposes to a repetition at a later date, we have no experience which is relative.

**New Cases, 1923.** The 8 new cases observed during the past nine months, we believe, show evidence of both structural and functional involvement of the heart, the relative degree of each factor varying in the individual case. We have, therefore, divided these 8 new cases into 2 groups of 4 each; the first with predominant structural involvement, in which definite and unmistakable evidence of organic heart involvement can be demonstrated with a lesser degree of functional symptoms; the second, in which the functional involvement predominates, while definite structural disease is either slight or questionable. The majority of these cases have followed acute influenzal infections or some complication thereof.

TABLE II.—CASES SHOWING PREDOMINANCE OF STRUCTURAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.
No. 9 Mrs. W.	Influenza; pneumonia	Subacute† myocarditis	Early heart failure	Partial A-V block	7.2% plus.
No. 10 Mrs. L.	Influenza; pneumonia; acute arthritis; empyema.	Subacute† myocarditis and endocarditis; mitral stenosis, aortic insufficiency	Moderately advanced heart failure	Partial A-V block; right bundle branch block	20.0% plus.
No. 11 Mrs. G.	Measles; diphtheria; epidemic influenza, 1919 Influenza; pneumonia	Chronic myocarditis† and endocarditis; mitral stenosis and regurgitation	Moderately advanced.	Sinus rhythm	20.1% minus.
No. 12 Mr. P.	Diphtheria 7; pneumonia 1918 Peritonsillar abscess (streptococcus) Pneumonia 9 years ago	Subacute endocarditis; mitral insufficiency; subacute glomerular nephritis	Moderately advanced heart failure	Sinus rhythm	12.8% plus.

\* Acute infections above, previous infectious diseases below the line.

† Not confirmed by histological examination.



**PREDOMINANT STRUCTURAL INVOLVEMENT.** The first patient of the "structural group" (Case IX) is a woman, aged thirty years, who developed, in October, 1922, a diffuse bronchopneumonia following influenza, during the course of which she showed a rapid,

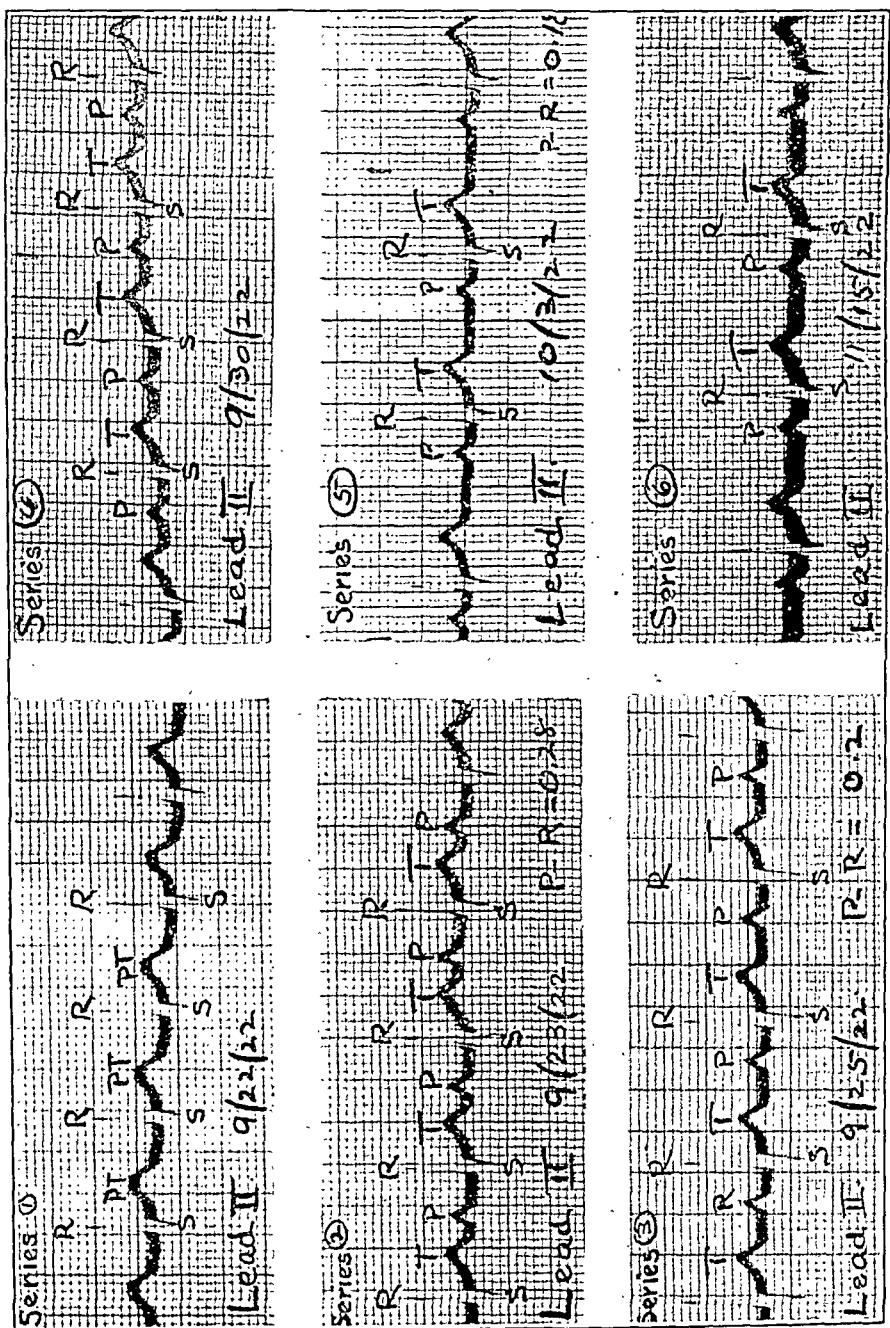


Fig. 4.—Case No. IX. Mrs. S. W., aged thirty years, housewife, influenzal bronchopneumonia, postinfectious subacute myocarditis with partial A-V heart block. Series of six electrocardiograms (Lead II) taken at varying intervals during course of infection (six months), from first series taken at the height of infection to last showing restoration of normal cardiac mechanism.

irregular pulse which proved to be a partial auriculo-ventricular block (Fig. 4). The discharge diagnosis was postinfluenzal bronchopneumonia, postinfluenzal subacute myocarditis with partial auriculo-ventricular heart-block. The heart was moderately enlarged to the left; the blood-pressure, 102/78.

This patient is still under observation. Her heart is now rapid, but regular and enlarged to the left. She still complains of marked dyspnea on only slight walking, precordial pain, has a very limited cardiac reserve; becomes quickly exhausted on slight effort and is

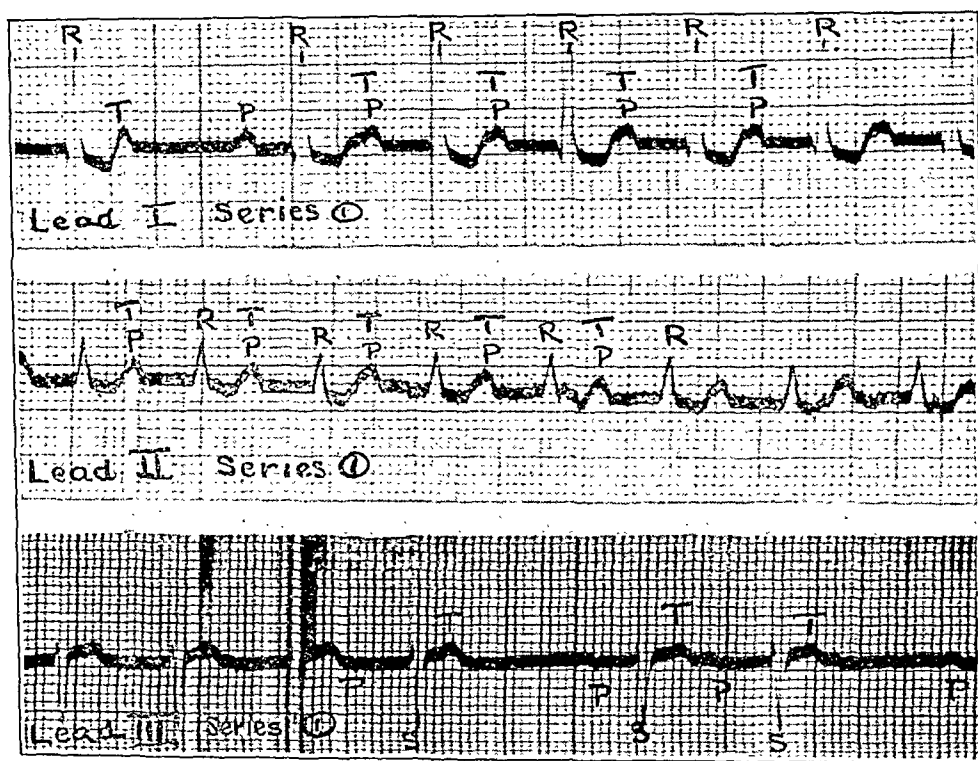


FIG. 5.—Case No. X. Mrs. E. L., aged twenty-six years, housewife, combined rheumatic and postinfluenzal heart disease, influenzal bronchopneumonia with empyema; postinfectious subacute myocarditis with partial A-V heart block, and right bundle branch block; subacute mitral and aortic endocarditis with mitral stenosis and aortic insufficiency. Tracing made September 13, 1922 (Series I), two months after onset of rheumatic infection and one month after onset of acute lung infection.

pale, gray looking and cyanotic. She had had no acute infectious diseases prior to her pneumonia. She is nervous, depressed, worries a great deal regarding her condition and runs an occasional slight afternoon temperature. We consider the partial auriculo-ventricular block, dyspnea, cyanosis and enlargement of the heart, and easy exhaustion, due to structural disease; the other symptoms, functional.

The second patient (Case X), a young married woman, aged twenty-six years, developed six weeks prior to her admission an

acute infectious arthritis and three weeks later an acute pleuritis with bronchopneumonia and empyema. She had measles, mumps and diphtheria as a child and influenza in 1919. The completed diagnosis was acute infectious arthritis, influenzal bronchopneumonia and empyema, postinfectious subacute endocarditis and myocarditis, with aortic insufficiency and mitral stenosis, partial auriculo-ventricular and bundle branch-block (Fig. 5). She had

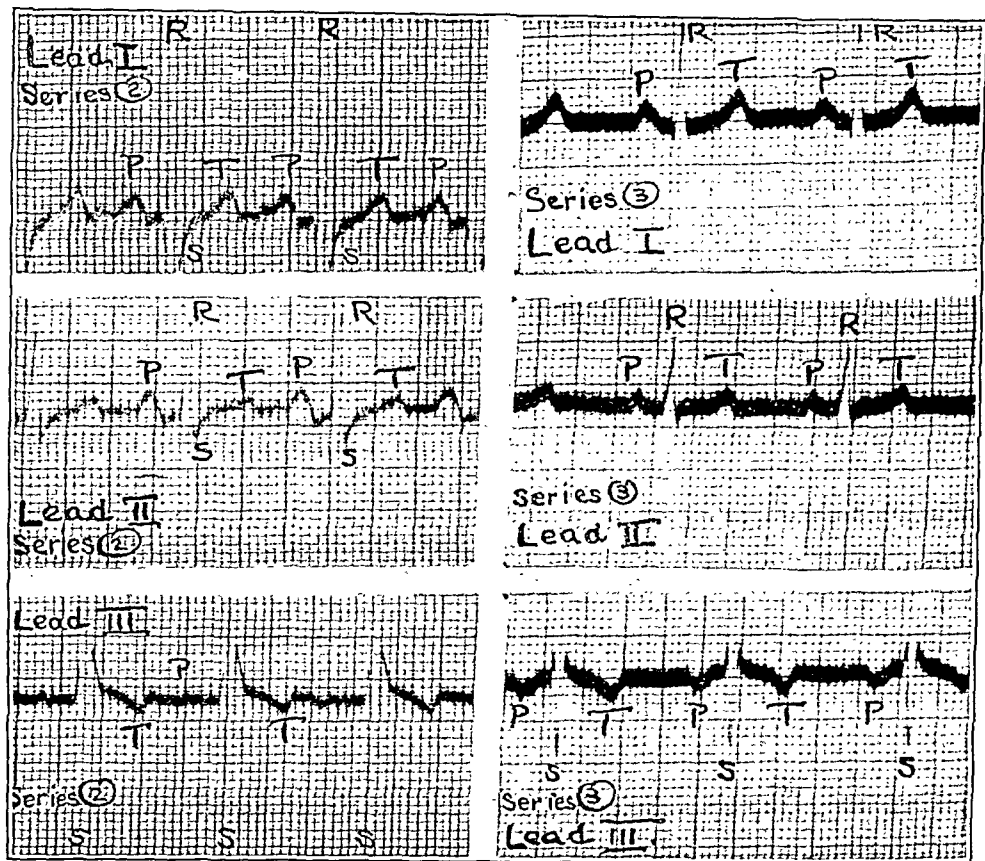


FIG. 6.—Case No. X. Mrs. E. L. Series (II) and (III), postinfectious A-V and bundle branch block; Series (II) made November 18, 1922, two months after Series (I); Series (III) made February 27, 1923; five months after Series (I). Both show disappearance of A-V and intraventricular block and gradual return to normal cardiac mechanism.

some evidence of thyroid involvement, her basal metabolism rate being 20 per cent plus, blood-pressure of 142/80 and pulse 112 (Fig. 6).

She apparently has completely recovered and is able to be out of bed and perform her household duties with no evidence at the present time of heart failure. This patient was extremely ill for many weeks; lost between 40 and 50 pounds in weight; was at times deeply cyanotic with orthopnea, with enlarged tender liver, etc.;

at all times frightened, depressed, apprehensive, complaining of insomnia, anorexia, etc. Her breathing and pulse were at times extremely rapid. She needed many months to regain her equilibrium, cardiac reserve and ability to walk about. We feel the mitral and aortic disease, conduction path involvement, dyspnea, heart dilatation and cyanosis are due to structural disease; many of the other findings, either functional (effort syndrome) or related to the thyroid involvement.

The third patient (Case XI), a married woman, aged thirty-five years, has early, slight heart muscle failure with mitral stenosis and regurgitation, apparently the result of epidemic influenza and pneumonia in 1918. Her blood-pressure is 120/80. When first seen she had limited response to effort, edema of ankles, cyanosis, decreased urinary output. On rest in bed and moderate amounts of digitalis, she apparently has completely recovered. Her findings are all structural in origin except the attacks of simple tachycardia, anxiety, depression, etc., which we interpret as being of psychogenic character.

The fourth patient (Case XII), a man, aged thirty-seven years, who, following a peritonsillar abscess in which hemolytic streptococcus was found, developed swelling of the feet and legs, decreased urinary output, pallor, dyspnea, rapid pulse and weakness. Blood-pressure varied from 140/100 to 157/92. His urine showed occasional blood, a large number of casts and considerable albumin. He had had pneumonia nine years ago. His right heart border was 3 cm. and the left 9 cm. from the mid-sternal line, with a soft pre-systolic and systolic murmur at the apex. He was diagnosed post-infectious heart disease, subacute mitral endocarditis with mitral insufficiency and stenosis and moderately advanced heart failure. His pulse at all times has been extremely rapid.

The electrocardiogram showed an inversion of the T-wave in the first lead. He is still under observation and is dyspneic on effort and is pale. The majority of his findings, we believe, are on an organic basis.

**SUMMARY.** These 4 cases, we believe, show that, as a result of these acute infections, various portions of the heart, endocardium and myocardium or both are involved, and that, although marked recovery has occurred during these early months, at least in 2 of them evidence of heart failure still exists. We conclude that acute influenzal infections cause structural damage to the heart, even as the older, better recognized infections, acute rheumatic fever, diphtheria, etc. We believe that following these acute respiratory infections, the development of valve murmurs (particularly diastolic), cyanosis, dyspnea, orthopnea, diminished urinary output, enlarged tender liver, auriculo-ventricular or bundle branch-block, enlargement of the heart to percussion, are clear evidences of organic disease. The fact that under adequate treatment most

or all of these findings are relieved, does not, we believe, speak against this view. The rather constant association of nervousness, depression, anxiety, insomnia, anorexia, occasional tremor, tachycardia, breathlessness, precordial pain, easy fatigue, are functional or thyroid in origin. Of particular interest, and emphasized here for the first time as far as we know, is the association of these two groups of findings in these patients suffering from the results of these acute respiratory infections.

**PREDOMINANT FUNCTIONAL INVOLVEMENT.** The following 4 cases show evidences of marked functional and questionable structural involvement of the heart.

TABLE III.—CASES SHOWING PREDOMINANCE OF FUNCTIONAL HEART INVOLVEMENT.

Case.	Etiological diagnosis.	Structural diagnosis.	Functional diagnosis.	EKG diagnosis.	B.M.R.	Neurological diagnosis.
No. 13 Mrs. S.	Influenza (epidemic 1918) * Diphtheria 9; chorea 13. Diarrhea with fever 3 and one and a half years ago	Subacute myo- carditis†	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	21.7% minus	Anxiety state.
No. 14 Mrs. F.	Puerperal infection; Cesarean section. * Diphtheria 5; typhoid 15. Epidemic influenza 1918; acute inflammatory rheumatism 1918	Subacute† myo- carditis	Early heart failure (?) effort syndrome	Low voltage; inversion and notching R3	14.9% plus	Major hysteria.
No. 15 Mrs. R.	Epidemic influenza (1918)	.....	Effort syndrome	Paroxysmal tachycardia	1.4% minus	Anxiety state.
No. 16 Mrs. B.	Epidemic influenza (1918) * Scarlet fever 4; typhoid 11	Subacute† myo- carditis Subacute thy- roiditis	Thyrotoxic heart	Low voltage; inversion and notching R3	17.1% plus	Hyperthyroidism.

\* Acute infections above, previous infectious diseases below the line.

† Not controlled by histological examination. Autopsy findings in similar cases show only dilatation.

The first patient (Case XIII), a married woman, aged thirty-five years, complains of occasional palpitation of the heart, attacks of pain under the left breast of three years' duration, the first attack occurring following acute diarrhea and fever three years ago. She had diphtheria at nine and chorea at thirteen years. Examination is essentially negative. Blood-pressure is 112/60 and basal metabolism 21.7 per cent below normal. She was diagnosed as post-infectious myocarditis (?) and anxiety state. The electrocardiogram showed an extremely low voltage in the third lead, with inversion of the initial ventricular complexes, a frequent finding in these postinfectious functional cases. Under preliminary rest in bed, later graded exercises, reassurance regarding her condition, alternating thyroid and bromide medication, she has made satisfactory progress.

The second patient (Case XIV), a married woman, aged twenty-nine years, complained of dyspnea, extreme nervousness and continuous temperature since the birth of her third baby five months

previous. She had diphtheria at five, typhoid at fifteen years, epidemic influenza and pneumonia in 1918 and acute infectious arthritis in 1918. She is a large, obese, pale and unhealthy looking woman. Her basal metabolic rate is 14.9 per cent above normal. The electrocardiogram is negative, except for the same low voltage and inversion of the *QRS* group, as in the previous case. She was diagnosed as postpuerperal myocarditis, major hysteria and sub-acute hyperthyroidism. She is somewhat improved at the present time.

The third patient (Case XV), a young married woman, aged thirty-five years, suffered severe, sudden, acute attacks of tachycardia, which we believe were true paroxysmal tachycardia, the first attack occurring four years ago following epidemic influenza. She has had no other acute infectious diseases. Examination is essentially negative, except that she is extremely thin and poorly nourished. The electrocardiogram is negative, except for low voltage in the third lead. Although she is improved, any severe emotional display is apt to be followed by an abrupt onset of her tachycardia.

The fourth patient (Case XVI), a married woman, aged thirty years, believes she has not been well since influenza in 1918 and again a "grippe" attack in September, 1922. She complained of an extremely rapid pulse, with failure to gain weight. She has no dyspnea. Examination shows an enlargement of the left thyroid lobe and a metabolic rate of 17.1 per cent +; pulse, 118, and blood-pressure, 144/88. She was diagnosed as postinfluenzal sub-acute myocarditis and thyroiditis with hyperthyroidism. Under complete rest in bed, bromides and occasional small amounts of digitalis, she has made a satisfactory gain. She had scarlet fever at four and typhoid at eleven years.

These 4 cases may be discussed together. We conclude that in view of the findings of palpitation, precordial pain, periodic attacks of nervousness, exacerbation of cardiac symptoms following emotional excitement, persistent tachycardia and breathlessness, presence of depression and anxiety states that this type of case following epidemic influenza is largely functional in origin of the group variously called irritable heart, effort syndrome, neuro-circulatory asthenia. The fact, however, that they failed to recover entirely under treatment directed to such functional disorder, but have recovered following prolonged rest in bed and digitalis, in addition to adequate psychological management, justifies the conclusion that a minor portion of their complaints are of structural origin.

Summarizing the significant facts in these two groups of cases we find the following: They all show the development of their cardiac symptoms following acute respiratory infections (influenza). The significance and interpretation of these cardiac symptoms are,

of two types, one structural and the other functional, the relative degree of each varying in the individual case, in 4 being predominantly structural, in 4 functional. The majority of these cases have secured either complete recovery or marked improvement, the result being attained by a combination of treatment directed toward both structural and functional disease. We believe, therefore, that in the evaluation of this type of cardiac trouble following epidemic influenza it is of service to consider in each case the possibility of such dual disease, as we have found with such consideration the effects of treatment are markedly enhanced. In other words, instead of attempting definitely to separate organic from non-organic findings, this series of cases presents evidence representing a dual involvement. We desire to point out this possibility in each instance of postinfluenzal cardiac disease.

Considering these 16 cases as a whole, our first group of 8 cases of three years ago and the present series of 8 cases observed this past year, we reach the following conclusions: Acute respiratory infections (influenza) may and frequently do produce cardiac symptoms. These symptoms are often caused by both structural and functional involvement of the heart. Structural involvement is recognized by delayed conduction time, partial, complete or bundle branch-block, enlargement (dilatation) of the heart, endocardial murmurs and signs of early heart failure. Functional involvement is recognized by palpitation, precordial pain, fatigue, weakness, nervousness, anxiety, depression, cyanosis, dyspnea, pallor, tachycardia. These two groups of symptoms may and frequently do coexist in the same patient, and it is this coexistence of structural and functional involvement which we wish to especially emphasize. Structural involvement is often evident at first, may be entirely overlooked and is often extremely transitory. Functional involvement appears later, often dominates the clinical picture and usually requires a longer period for relief.

**Conclusions.** 1. A reconsideration of 8 cases of postinfluenzal cardiac disease, first observed and reported in 1920-1921, shows 5 completely recovered, 2 not traceable and 1 unimproved.

2. Eight new cases of cardiac involvement following acute respiratory infection observed during the past nine months present evidence of both structural and functional involvement, half predominant structural, half functional.

3. Diastolic murmurs, enlargement of the heart to the left, swelling and tenderness of the liver, edema of ankles and diminished urinary output, auriculo-ventricular and bundle branch-block serve as criteria of structural disease; palpitation, tachycardia, precordial pain, nervousness, depression and anxiety states are suggestive of functional involvement; breathlessness, cyanosis, weakness, exhaustion and fatigue are of indeterminate interpretation and significance.

4. The possibility of coexistent structural and functional disease should be borne in mind in a survey of any postinfectious heart patient. Treatment directed toward amelioration of both types of symptoms offers not only the most favorable chance of recovery, but may be of differential diagnostic value.

5. Delayed conduction time, partial, complete or bundle branch-block occurring at the height of an acute respiratory infection may be interpreted as structural heart involvement. The fact that such findings may be based upon extremely slight or negative histological findings and are transitory in character does not of itself speak against this view.

6. It is desired especially to emphasize the coexistence of structural and functional involvement of the heart (following influenza) in the same patient. Structural involvement is often evident at first, may be entirely overlooked and is often extremely transitory. Functional involvement appears later, often dominates the clinical picture and usually requires a longer time for relief..

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#### DETAILS IN THE TREATMENT OF HAY-FEVER, ASTHMA, AND OTHER MANIFESTATIONS OF ALLERGY.\*

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THE development in our knowledge of the subject hypersensitiveness, its diagnosis, and treatment, marks an important advance in the theory and practice of medicine. Through acquaintance with this sphere of work, we are now able to understand and relieve many kinds of illness which in previous years were looked upon as obscure in origin, and not amenable to treatment.

Illnesses caused by hypersensitiveness to foreign substances, can be treated along five different lines, namely: Avoidance or removal of the specific cause of illness; avoidance or removal of contributory causes; specific protein treatment; non-specific protein treatment; symptomatic treatment.

Each of these measures is important. The choice depends upon the severity of the illness, upon the degree of hypersensitiveness, and upon the nature of the substance to which the patient is hypersensitive. In the majority of cases, two or more of the above measures can be used to advantage. The simplest method is best when the simplest can be used—namely, avoidance or removal of the specific cause of illness. However, removal of the specific cause is often difficult or impossible. This is true in the case of

\* Read in brief before the Chicago Medical Society, February 28, 1923.



sensitiveness to the common pollens, to common foodstuffs (milk, eggs, and wheat), to products originating in the body which cannot be removed, and to substances which cannot be discovered by means at our disposal. In these instances, one or more of the latter four measures must be chosen.

**Removal of Cause.** Having ascertained the fact that a patient is sensitive to a certain substance, it is important to know whether the clinical symptoms occur as a result of direct contact between the substance and the affected tissues, or occur as part of a general reaction. For example, in the case of asthma caused by sensitiveness to wheat, it is important to know whether the respiratory symptoms result from direct contact between the mucous membrane of the bronchial tubes and wheat flour inhaled, or whether they occur as part of a general reaction due to the ingestion of wheat bread. In the former case, bread can be eaten with impunity and the patient, to be relieved, needs only to avoid contact with wheat flour. In the latter case it may be necessary to remove wheat from the diet.

It is, furthermore, important to know whether an individual is sensitive to a given substance as encountered in its natural state only, or whether he is also sensitive to the substance after it has been cooked. For example, an individual sensitive to lactalbumen, is made ill by raw milk, but tolerates unlimited amounts of cooked milk. In the case of sensitiveness to egg white, an individual can tolerate cooked egg. In sensitiveness to ovomucoid, however, he may be made ill by either raw or cooked egg.

The ocular, nasal, and bronchial symptoms, and eczema confined to the hands, face, and ankles are in the majority of cases attributable to direct contact between the mucous membrane or skin and the substance to which it is sensitive.

Urticaria, angioneurotic edema, generalized dermatitis, bladder allergy, hypotension, and neurological manifestations usually occur as part of a general reaction. Air carried allergens are rarely absorbed in sufficient quantity to give rise to these general symptoms, although this does actually occur occasionally. As an example, I may mention a case of autumnal hay-fever in which the dominating symptoms were neurological.

Gastro-intestinal manifestations may result from local contact of the mucous membrane with a food or may occur as readily as part of a general reaction after absorption of an offending food product.

As a rule, a symptom such as asthma, occurring as part of a general reaction, is frequently associated with other manifestations of general reaction such as hives, angioneurotic edema, etc. This is not true of the same symptom, asthma, when it occurs as a local reaction, that is as a result of local contact of the bronchial mucous membrane with air-carried substances. Bearing in mind this gen-

eral rule, it is often possible to surmise correctly that a symptom, such as asthma, hay-fever, or eczema, is due to exposure to some air-carried substances, or to a food which has been eaten, or to some product which has been elaborated in the body. A knowledge of this fact is often useful in the attempt to relieve the patient.

**POLLEN.** Pollen can usually be avoided by a change in geographical situation. In the case of sensitiveness to light air-carried pollen of the common weeds which pollenate over a long season, complete avoidance can hardly be accomplished otherwise. Pollen can be avoided in sufficient degree to give relief in mild cases by removal of the common weeds of the neighborhood, by having the patient confine his activities to downtown districts, by avoidance of trips in the country, by having him live and work on the upper floors of office buildings or hotels, and by having him keep the windows closed. This often gives partial or complete relief in mild cases, except on windy days when the air is filled with pollen even at the top of high buildings. Scheppëgrell's ingenious experiments have shown the marked effect of a strong wind on the distribution of pollen in the air at different heights.

In the case of sensitiveness to rare pollens such as choreopsis, relief can easily be obtained by avoidance of districts in which the flowers grow profusely, or by having them removed from the immediate vicinity.

**PRODUCTS OF VEGETATION OTHER THAN POLLEN.** Products of vegetation other than pollen, can usually be avoided easily if the source of the illness is recognized. Orris root is worthy of especial mention since this product is so widely used in the manufacture of perfumes, flavoring extracts, toilet articles of all sorts, including tooth paste, face powder, and soap.

In the case of sensitiveness to the stalk or leaf of plants, such as clover or straw, the offending substance, as a rule, can be avoided sufficiently to relieve symptoms if the patient is aware of the source of his trouble. Clover, on account of its profuse growth, is difficult to avoid entirely; but, according to our experience, the degree of sensitiveness is not extreme in grade so that its complete avoidance is not necessary.

The essential oils and other products of plant life such as turpentine, cedar oil, the oils used in perfumes and flavoring extracts, also the products derived from coal, such as benzol and those derived from crude oil, such as gasoline, can usually be avoided easily if recognized as a source of illness.

**Food.** The symptoms of food idiosyncrasy usually occur as part of a general reaction to a food or a split product. In the case of sensitiveness to uncommon articles of diet, such as tomato, onion, and cabbage, avoidance is simple. When a patient is sensitive to articles used so commonly in cooking, as milk, eggs, or wheat, avoidance is difficult, especially if he is sensitive to the

cooked as well as the raw product. It is rarely advisable to attempt specific treatment in a case unless sensitive to cooked milk, egg, or wheat.

**ANIMAL PRODUCTS.** It is rarely advisable to treat specifically for sensitiveness to animal dander such as horse, cat, or dog, since the animals and their pelts can usually be avoided. In several cases of sensitiveness to wool (all eczemas) observed by the writer, the symptoms were not severe and were relieved through the use of cotton clothing between the skin and woolen garments.

Walker has obtained splendid results in increasing tolerance for animal dander, by subcutaneous inoculations with dander extracts. He does not recommend this treatment when avoidance is possible. In sensitiveness to feathers, such as goose, duck, or chicken, relief can be obtained by the use of floss pillows. This type of sensitiveness is rather rare in my experience.

**DRUGS.** When individuals are sensitive to drugs, such as iodoform, formalin, novocaine, morphine, aspirin, etc., relief of symptoms can be obtained if the cause is discovered. One is occasionally sensitive to an impurity in a drug. This is important in the case of drugs so useful as acetyl salicylate and arsphenamine for an individual sensitive to one preparation of a drug can often tolerate other preparations.

**HOUSE DUST.** House dust is worthy of especial mention since it is frequently responsible for house asthma, the importance of which has been especially emphasized by Cooke. Relief can often be obtained by the removal of certain articles of furniture, upholstery, rugs, disinfectants, cleaning fluids, glue, etc.

In one interesting case, observed by the writer, sensitiveness was traced to wood smoke. It was found the patient could live comfortably only in steam heated apartments and that she invariably had severe asthma in houses where open fires or furnaces were used. She was so affected even during the summer months when the furnaces were not in use.

**SMOKE.** Individuals sensitive to smoke can frequently obtain relief by slight change in environment. One patient who had asthma due apparently to gasoline smoke, could invariably obtain relief by moving to a different part of a hotel in which he lived. The room which he occupied at the time of his illness was situated directly over the garage. Individuals sensitive to coal smoke should be cautioned against long railroad trips, since in this position they are frequently exposed intensely to smoke and may suffer a severe exacerbation of their illness.

**BACTERIA.** Definite symptoms of allergy often accompany acute infectious diseases, such as rheumatic fever and scarlet fever. These manifestations can be treated best symptomatically since they often disappear spontaneously after the acute illness has subsided. Individuals sensitive to products elaborated in chronic

foci of infection, should be treated by removal of such foci. When the focus cannot be reached, however, treatment with vaccines is justifiable. According to Walker and Rackemann, this method of treatment frequently yields beneficial results.

**THERAPEUTIC SERA.** In demonstrated hypersensitiveness to horse serum, the therapeutic use of horse serum is dangerous even in very small doses and should not be used. Antitoxins of sources other than horse should be provided for patients of this type. Patients sensitive to horse dander are not necessarily sensitive to horse serum. If there is any question whatever, intracutaneous tests should be made before serum is administered.

**BLOOD TRANSFUSION.** I have observed 2 cases of collapse at the beginning of blood transfusion, both relieved by the hasty use of adrenalin. In each case the bloods had been tested with great care for compatibility, so far as agglutinins were concerned. Upon inquiring into the cause of the collapses, it was found in 1 case that the patient came from a hypersensitive family, had suffered from asthma due to milk, and gave positive intracutaneous tests with lactalbumen. The second patient was sensitive to tomato and cabbage. In each case the donor had eaten foods to which the patients were sensitive and no such results followed the use of other donors. The reactions were believed to be due directly to sensitiveness on the part of the patients to foods eaten by the donors. The statement, while seemingly fantastic, appeared to us actually very real, and would seem analogous to the eczema of breast-fed babies caused by sensitiveness of the infant to certain foods eaten by the mother.

**LIGHT.** One patient observed by the writer was specifically sensitive to violet light or the violet rays of white light; or better stated, sensitive to some product elaborated in the tissues under the influence of light. She would become ill invariably if exposed a few moments to sunlight. Exposure of the skin to either sunlight or light of a nitrogen lamp or light filtered through violet glass would give rise to erythema in less than three minutes and to a wheal covering the entire area exposed in five and a half minutes. Roentgen-ray, actinic-ray, heat, colored light (except violet) and several kinds of mechanical and chemical irritants produced no noticeable effect. She was completely well when protected from light. Her skin was rendered tolerant in one locality by repeated exposure to light so that she could tolerate a ten-minute exposure in this locality with apparently no change in the skin. After several weeks the tolerance gained in this way was lost. Our complete study of this interesting case has been reported in another communication.

**MULTIPLE SENSITIZATION.** Patients sensitive to a number of substances may tolerate some of them if the others are carefully avoided. For example, many patients with pollen hay-fever give positive

skin tests to vegetables, fruits, or grains and actually obtain partial relief of hay-fever by avoidance of the food products to which they give positive tests. These substances may have no untoward effect except during the pollen season. One patient with hay-fever and eczema was found sensitive, among other things, to a certain silk dress. An extract from the dress gave an intensely positive cutaneous test. It was observed, however, that when her illness was relatively mild due to the avoidance of other substances which made her ill, she could wear the silk dress with impunity. At other times, however, when she was suffering markedly with hay-fever, and dermatitis, the wearing of the dress invariably caused itching and an increase in the rash and asthma.

**SUMMARY.** To recapitulate, the avoidance or removal of the specific cause of reaction is the simplest and surest method of treatment when this can be accomplished. It is only in cases where the specific cause is not discovered or cannot be removed that the measures to be described subsequently need be resorted to.

**Removal of Contributory Causes.** Very frequently it is impossible to discover the specific substance primarily responsible for the manifestations of allergy. In this case, removal of certain contributory causes may relieve the patient partly or completely.

**PHYSICAL FACTORS.** Physical factors which definitely add to the symptoms of reaction and often determine their site of localization, are divided by Walker, into mechanical, chemical, odorific, and thermal. To this may be added reflexes and functional activity as common contributors. The untoward effect of these factors has been mentioned by many observers and is noticed by a large proportion of sensitive patients. For example, patients subject to urticaria are frequently relieved to a marked extent by the removal of agents which irritate the skin mechanically; by the avoidance of agents which cause increased activity of the glands (sweating); by protection of the skin from heat or cold and by the avoidance of irritating lotions.

Similarly, patients who have dyspepsia and abdominal pain as a result of alimentary reaction, can often obtain partial relief by the avoidance of foods, such as nuts, which irritate mechanically; by the avoidance of substances such as coffee, and alcohol, which stimulate functional activity; by the avoidance of condiments, such as mustard and pepper which irritate chemically; and by the removal of the source of abnormal reflexes, such as a diseased appendix or gall-bladder.

Likewise, patients who have asthma are often relieved to a marked extent by the avoidance of dust, irritating vapors, the odor of flowers, essential oils, or perfumes; by living in a dry climate; and finally, by the correction of pathological defects in the nose or gastro-intestinal tract or other localities which give rise to pathological reflexes.

**PATHOLOGICAL FACTORS.** Patients who are ill with symptoms of reaction (especially general reaction) are occasionally relieved completely by another disease. I have observed 3 cases of asthma who apparently were permanently relieved by severe infectious diseases—erysipelas in 2 cases and scarlet fever in 1. As a rule, however, additional illnesses make the symptoms worse. Frequently asthma starts after an acute infection, an operation, especially intranasal operations, or other illnesses. Asthma is almost always made worse by infections in the respiratory tract. Many individuals subject to asthma have asthma only during and for several weeks following attacks of acute rhinitis, bronchitis, or sinus infection. Alimentary reactions are usually made worse by ulcer, gall-bladder disease, or chronic appendicitis. Very often partial or complete relief can be obtained by attention to these conditions.

Dysfunction in the glands of internal secretion, which is rather frequently noticed (in cases of general reaction) often adds to the severity of the illness, and treatment of these conditions may give partial relief.

**SUMMARY OF CONTRIBUTORY CAUSES.** To recapitulate, when one fails in his effort to find or remove the specific cause of illness, frequently his only recourse lies in paying attention to other abnormalities and illnesses with which a person may be afflicted. A serious, careful effort in this line often gives relief, which can be obtained in no other way.

**Specific Protein Treatment.** In view of our knowledge of the tolerance which can be developed in patients or animals for living bacteria by subcutaneous inoculation with their products, and in view of the fact that hypersensitiveness to serum in animals can be completely removed by inoculations with serum, it has been quite natural that many investigators working both jointly and independently should have tried this method of treatment on human beings sensitive to pollen and other bodies, not of bacterial origin. These researches have been described under the terms anaphylaxis, protein sensitization, allergy, specific hypersensitiveness, etc.

It is good fortune that tolerance for foreign substances can frequently be developed in this way in sensitive patients, and it is surprising that statistics published by different writers using different plans in therapy agree in the essentials concerning the results which can be obtained. For the many names and researches responsible for the development of this line of knowledge, the reader is referred to the authors mentioned in the bibliography.

**POLLEN TREATMENT.** The practical development of this line has been due to the efforts of a number of investigators, among whom may be mentioned, Curtis, Dunbar, Noon, Freeman, Koessler, Lowdermilk, Rackemann, Walker, Cooke, Scheppegegrell, Goodale,

and others. The method generally employed lies in the use of increasing doses of pollen extract given subcutaneously at varying intervals of time. An increase in tolerance for pollen is the result in the majority of cases with partial or complete relief of symptoms. The writer has used this method each year since 1915, trying different plans in technic each year. The results have been approximately the same, with perhaps some improvement each year until the use of local applications of pollen solution to the nasal mucous membrane was added last year. This increased very materially the number of good results. The following plans, in brief, were employed.

*First Method.* Whole pollen of small ragweed, large ragweed, and golden rod, equally mixed, ground finely and suspended in Lowdermilk's solution was used for the inoculations. This solution was prepared at frequent intervals due to a belief that pollen solutions had a marked tendency to deteriorate even at ice-box temperature. The maximum dose given was 1 mg. of pollen.

*Second Method.* The second method was like the first except that the solutions were purified by centrifugation at high speed.

*Third Method.* Several pollens were each weighed out separately in 10 mg. lots and kept in wax papers in a desiccator. A specimen of each was ground up finely at weekly intervals, suspended in Lowdermilk's solution and given in increasing doses, each patient being given the pollen to which he was sensitive. The use of this method seemed to yield better results than the previous ones.

*Fourth Method.* Each of some twenty pollens, common to this district, were ground up separately with sand in 500 mg. to 5-gram lots, were suspended in Lowdermilk's or Coca's solution, (1 per cent suspension) and clarified after several days by sedimentation. Toluol was added to this mixture last year (at Coca's suggestion) as a preservative. This preparation seemed to keep potent for several months at ice-box temperature. Its use saved the laborious process of preparing fresh suspensions each week. (NOTE. The plan of making suspensions sufficient in quantity to last an entire season is recommended since by its use the preparation of fresh stock solutions of somewhat greater potency than the old ones is avoided. Coca's method of filtering his preparations through a stone filter seems a valuable addition in technic, although no infections were obtained through our use of stock solutions as above prepared.)

From each stock solution, serial dilutions were made at weekly intervals and kept at ice-box temperature. In the treatment of patients those extracts were chosen for use which produced a positive conjunctival reaction in a 1 to 1000 dilution. When none of the pollens gave positive conjunctival tests, as happened in several instances, those pollens were chosen which gave the strongest intracutaneous tests. The following plan of administration was used:

Treatment was commenced, when possible, in June. In many instances, treatment was started much later than this, and even at the beginning of and during the pollen season. For the initial dose 0.1 cc of a solution containing 0.001 mg. of pollen to the cc was used in every instance. The injections were given each day and the dose doubled each day, that is, patients were given 0.1 cc on the first day, 0.2 on the second, 0.4 cc on the third, 0.8 cc on the fourth, and on the fifth 0.1 cc of solution ten times as strong, that is, a dilution of which 1 cc contained 0.01 mg. of pollen. This increase in dosage and concentration of solution was continued until a dose of 0.25 cc to 0.5 cc of a 1 per cent solution was reached—that is, a solution of which 1 cc contained 10 mg. of pollen. When this, the maximum dose, was reached, the interval was spaced out to from three to six days, and this dose was repeated when possible up until a few days before time for the pollen season to commence. It was then discontinued. When there was need for haste because of the approach of the pollen season the injections were given twice daily instead of once daily. These patients gained tolerance more rapidly and reacted less it seemed than the others. This method, I believe, will become the method of choice.

Patients who failed to show signs of hay-fever after the season was well started were given no further treatment. Those who developed hay-fever, however, or who seemed to be less than 75 per cent relieved, or who had been insufficiently treated subcutaneously because of starting late, were given local treatments in the following way:

*Local Treatment with Pollen.* At daily intervals a mixture of several 1 per cent suspensions of the more important pollens of this district, namely, the three ragweeds, cocklebur, sages, marsh-elder, and lamb's-quarter, were sprayed into each eye and into each nostril. Following this there was almost invariably a marked attack of hay-fever, which in some instances, required adrenalin locally for relief. After this administration had been given for a few days, the reactions after treatment, almost without exception, became less marked, and after 5 to 10 treatments, disappeared almost completely. At the end of 10 treatments, the patients were almost without exception relieved of hay-fever, or partly relieved. The treatments were discontinued when marked relief was obtained. The mixture of pollens as above mentioned was used in preference to solutions of the individual pollens because of a belief that pollens other than the ones which gave positive tests might have played contributory roles in the causation of symptoms. Patients sensitive to pollen not contained in the mixture were treated with the pollens to which they reacted.

*Modifications to Avoid Reactions.* While the plan of subcutaneous treatment, as above described, was carried out when things went smoothly, it was by no means adhered to in every case, especially



in patients who had not arrived at a high dosage before the pollen season commenced. In more than 50 per cent of the cases the treatment was modified on account of a tendency to react or on account of our fear of the same, and the dose of pollen was either increased less rapidly, repeated, or even reduced in amount at times. Often, also, the intervals between injections were lengthened. In individuals whose local reaction did not subside almost completely within twenty-four hours, the time interval was as a rule lengthened to forty-eight hours or even to three or four days. The endeavor was made not to give a dose until the effects of the previous one had almost entirely worn off.

The above plan of treatment is not recommended to physicians who are not thoroughly experienced in the use of pollen, since pollen reactions can be very severe, alarming, and even dangerous. Whereas we have never as yet had a mishap nor an alarming reaction in pollen therapy, we attribute this partly to the fact that patients have not been allowed to leave the office for a half to one hour after receiving injections and adrenalin has been administered freely and quickly whenever signs of reaction appeared. It has been due also to the fact that we have avoided increasing the dose of pollen too rapidly and have avoided making the interval between injections too short in patients in whom a tendency to react was noticed. The above plan is safe I believe in the hands of physicians experienced in pollen therapy; in fact, our severest reactions have not been obtained with the higher doses of pollen nor in patients in whom this plan was carried out perfectly, but in patients who, for some reason, did not take treatment regularly and in patients who were being tested intracutaneously. Patients who stop therapy for two weeks or more are likely to react strongly when treatment is resumed unless the dose is reduced.

In addition to the pollen treatment as above outlined, patients who gave positive intracutaneous tests to fruits, vegetables, grains or dander (and this was true of the great majority of patients) were asked to avoid during the pollen season those substances to which they gave positive skin tests. Some of the patients noticed, on testing themselves out, that such substances caused an actual increase in their tendency to have hay-fever. Others noticed no untoward effect. In the latter case, they were allowed to choose any diet they desired.

In addition to this, patients who had a tendency to have hay-fever were advised to wear goggles at times (even at night) when they were exposed to pollens; to avoid pollen so far as possible by keeping in downtown districts, keeping the windows closed, and avoiding trips in the country, railroad trips, etc., and to apply the following lotion to their conjunctiva and nasal mucous membrane when needed: Adrenalin (1 to 1000 solution), 1 cc; resorcin solution (3 per cent), 31 cc.

It is important also for patients with a tendency to pollen asthma to avoid mouth-breathing if possible, for frequently when the nose is stopped up and mouth breathing is practised, pollen asthma will start.

*Theoretical Reasons for the Above Methods of Therapy.* One's first impression of pollen therapy is that it is analogous to vaccine therapy. One is inclined, therefore, to follow methods learned from the use of vaccine and tuberculin therapy. This is a mistake, for pollen therapy and vaccine therapy are quite different. The reaction from vaccine injections appears slowly—that is, after a period of hours. Also, the immunity gained appears slowly—that is, after a period of hours or days. The reaction in an allergy patient, however, after an injection with pollen appears almost immediately—that is, in a matter of minutes or seconds. Tolerance likewise appears quickly. This is true not only of pollen when given subcutaneously but also when applied locally. For this reason, one should expect a better result from injections when given at shorter intervals.

Local applications of pollen solution were made on the basis of a report by McKenzie, who found that the intracutaneous injection of allergen in a sensitive patient gave rise to increased tolerance in the skin around the inoculated area. The writer had an excellent opportunity of verifying this work through the study of a patient whose skin was highly sensitive to light. It was observed in this patient that the application of winter afternoon sunlight to the skin for a period of two and a half minutes gave rise to a hive which would cover the entire area exposed. This gave rise to local immunity in the exposed area so that further exposure the same day would cause less reaction. The immunity so gained was lost after twenty-four to forty-eight hours. Repeated exposures on consecutive days gave rise to a high grade of local immunity so that eventually a twenty-minute exposure would give rise to less reaction than originally followed a two-and-a-half-minute exposure.

Inasmuch as the reaction and immunity appeared so quickly in the light case and inasmuch as reactions appear so quickly after subcutaneous treatment with pollens, it seems more logical to give the pollen at frequent intervals than it does at longer intervals. One is more likely thus to give his injections during a period of relative tolerance and reactions should be less frequent and less severe. This actually appeared to be the case in my experience for during one entire season this year we did not have one single marked constitutional reaction. In previous years one reaction was obtained on an average for every second case or for every sixtieth dose of pollen. These reactions appeared, as a rule, however, in patients who did not receive pollen treatment regularly

and occasionally, no doubt, was due to the injection of a small amount of extract into a capillary or venule.

*The advantages in the above plan in therapy* lies chiefly in the rapidity with which patients can be given tolerance for pollen. The giving of pollen at greater intervals with smaller rate of increase in dosage lengthens greatly the time required for treatment. Months are required before any marked grade of tolerance is established. It is difficult to keep patients under observation for prolonged periods and this treatment carried out with the help of physicians inexperienced in pollen therapy is notoriously unsatisfactory. By the use of daily injections the dosage can usually be increased rapidly to the point where concentrated solutions can be used.

*Treatment of Reaction.* It is a good rule to keep patients in the office for one hour after the injection of pollen extracts. If they complain of itching or redness of the skin, swelling of the tongue, a feeling of oppression in the chest, cough or wheezing, or of symptoms resembling hay-fever or of pain in the back, 0.5 cc of adrenalin (1 to 1000 solution) subcutaneously should be given immediately. If the reaction shows no sign of abating within three or four minutes, this dose should be repeated. If no signs of improvement occur within several minutes it should be repeated a third time or oftener. Atropine  $\frac{1}{100}$  grain subcutaneously should also be used. We have never observed a single reaction within a period of seven years, which has not responded readily to treatment administered in this way.

*Results of Pollen Therapy.* No results are more irregular than those which follow pollen therapy, unless treatment is adequately and carefully administered. When treatment is adequately administered, few fail to get partial or complete relief if the correct pollens are used. If treatment is inadequately administered, the percentage of cases relieved, hardly reaches 50 per cent.

Of the cases treated in our clinic last season, 62 in number, only 10 per cent failed to get marked relief. None of this 10 per cent were given local treatments in the nose. They had received adequate subcutaneous treatment, however. Of the cases which had received subcutaneous treatment 39 per cent returned after the beginning of the pollen season with symptoms of hay-fever, although as a rule not so severe as usual. The remainder were either free of symptoms, or so nearly free that no further treatment was given. Of the 39 per cent who were not relieved, practically all who received intranasal treatment were relieved partially or completely. Four cases who were relieved at the beginning of the season developed symptoms, although milder than usual in grade, toward the end of the season.

It has appeared to us on the whole, that patients with pollen hay-fever and asthma are as a rule either relatively easy to relieve,

or rather difficult to relieve. Of the former group, pollen therapy according to almost any plan seems to give partial or complete relief. Relief seems to persist, in many cases, for several seasons. Of the latter group, that is, the group who are difficult to relieve, the use of intranasal treatments increased the ratio of success more than any other modification of the method which we have ever used.

It is impossible to surmise in advance, which patients will be relieved most easily and to what extent treatment will have to be pushed. For example, one patient who had been subject to pollen hay-fever for forty-five years and who had never been able to obtain relief, except by a very wide change in geographical situation, gave one of the best therapeutic results from subcutaneous treatment alone. She was given 25 doses of pollen extract subcutaneously with maximum dose of 0.5 cc of a 1 per cent suspension of pollen and reacted mildly several times so that the routine had to be modified. In spite of this, she was so relieved of her sensitiveness, that she did not require local applications of pollen, and was able to disregard any of the weeds in her locality during the entire pollen season.

Another patient, who had been subject to severe hay-fever for a number of years, came for treatment several days after the pollen season had commenced. He gave a marked constitutional reaction which required adrenalin when the intracutaneous tests were applied. He was given shortly afterward an intranasal and ophthalmic treatment with pollen extract. He could not take further treatment of any sort. His hay-fever disappeared completely, however, after the reaction to pollen extract subsided and he went through the remainder of the season symptom-free.

Another patient, who had been subject to hay-fever and asthma of great severity for many years, was given 16 injections of pollen extract with a maximum dose of 1 mg. of pollen in 1916. He was given a series of 21 doses the following year with a maximum dose of 1 mg. He has remained clinically free of both hay-fever and asthma since the treatment was originally started.

*Summary of Pollen Therapy.* Whereas, marked irregularities in result are interesting and rather frequent, it can be said in summarizing, that the more consistently pollen treatment is given, the better the result is likely to be, and that if a patient is treated thoroughly with pollen subcutaneously and intranasally, a bad result should make one suspect an error in diagnosis.

**Specific Therapy with Proteins other than Pollen.** My experience in the specific treatment of hypersensitiveness with proteins other than pollen is rather small and has been confined to therapy with milk and egg. It has been possible in the majority of our cases for the patient to avoid substances responsible for illnesses, so that specific therapy was not necessary. This type of therapy

has not been so successful on the whole as therapy with pollen extract. This is believed to be the case for a very good reason. Patients who react to pollen are sensitive to the substance as encountered by the patient, while patients sensitive to a food may be sensitive to a digestive product. In the latter case, subcutaneous treatment with the protein as prepared in a laboratory would seem theoretically illogical. Treatment by mouth should offer more hope of success. In one patient sensitive to milk, tolerance was so increased by subcutaneous treatment and treatment by mouth that he was eventually able to take almost unlimited quantities of milk without his original symptoms, hives and asthma. A new symptom, however, namely diarrhea, began to follow the ingestion of milk.

In a patient sensitive to ovomucoid a few drops of a very dilute solution of egg by mouth or hypodermically caused asthma. Tolerance for egg subcutaneously was increased to a point where he could stand a relatively large dose without ill effect. It was never possible, however, to increase his tolerance for egg by mouth to a point where he could take more than 8 drops of a solution prepared by mixing 1 drop of whole egg with 250 cc of salt solution. Treatment by mouth was carried out faithfully by the mother over a period of six months but ended in failure.

**Non-specific Protein Treatment.** In spite of one's like or dislike for the use of arbitrary remedies in the practice of medicine, it is in the present state of our knowledge advisable to use them at times. This may be said of non-specific protein therapy in the treatment of allergy. Non-specific protein therapy can occasionally be used with a fair or even brilliant therapeutic result in the treatment of chronic asthma, chronic gastro-intestinal disturbances, eczema, and other disorders (occurring as part of a general reaction) when no other rational line of therapy presents itself. It is not recommended in the treatment of local reactions due to contact. It is excusable today to try it in general cases when the primary source of this disorder cannot be found or removed, or if no other more logical method of therapy presents itself.

It is not necessary to discuss non-specific protein therapy broadly in this connection. Suffice it to say that it has an influence upon immunity and, under certain circumstances, has an influence upon the functional activity of organs supplied by the vegetative nervous system. The following case is cited to illustrate how marked this influence may be.

The patient, a woman, aged thirty-five years, had been for many months, a victim of dyspepsia. The appendix and the gall-bladder had been removed. The stomach and duodenal bulb had been found anatomically normal at operation. At the time she came to me she was complaining of pain in the epigastrium, worse after eating, and associated frequently with nausea and vomiting. The

pain was brought on by almost any type of food, especially if taken in more than very small amounts. She had at the same time, colon bacillus pyelitis and cystitis. The stomach upon fluoroscopic examination showed a high grade of spasticity and hyperperistalsis; in fact, in this respect, it exceeded any which I have examined. The picture was that of four or five large balls of barium which extended across the abdomen. During the treatment for pyelitis, she was given a small dose of autogenous colon bacillus vaccine subcutaneously. She had a profound reaction after this with chill, high fever and general malaise. She returned the following day to say that her stomach had been cured by the vaccine. It was examined again and was found to have changed from its previous condition of spasticity into a relaxed bag, which almost filled the abdomen. Peristaltic waves were hardly visible. Food no longer caused discomfort or nausea and the patient suffered no marked gastric disorder for months.

Without discussing the mechanism through which non-specific protein therapy may exert its influence, suffice it to say that under certain conditions it has the practical effect of modifying the activity of certain organs supplied by the vagus and sympathetic nerves. Upon this basis I have used it occasionally as a remedy in the treatment of asthma, gastro-intestinal neurosis, dermatosis, and other general manifestations of allergy. The following case is cited as an example of the effect it can have in asthma.

The patient, a woman, aged fifty years, was brought into my office by the police with the statement that she had fallen unconscious on the street and was thought to be in a dying condition. She proved to have a very severe case of asthma of unknown origin and of long standing. She was given palliative remedies with a little temporary relief. She was later given 10,000,000 colon bacilli intravenously. A reaction followed with chill, high fever, malaise, and other symptoms. At the height of the reaction the bronchial tubes relaxed and she was able to breath freely for the first time in weeks. She remained nearly free of symptoms for about two months when her asthma recurred.

We have chosen colon bacilli for use in non-specific protein therapy because patients are almost always sensitive to colon bacillus protein and it seems to be the reaction which does good. Colon bacillus injected intracutaneously almost always gives rise to a marked local inflammatory reaction within twenty-four hours. If injected subcutaneously or intravenously in small doses, it almost always gives a marked constitutional reaction. As a rule, the subcutaneous treatment is preferable. If this fails a smaller dose, roughly one-fifth to one-tenth the subcutaneous dose, can be used intravenously.

The effect of this treatment, while occasionally very beneficial, is rarely permanent. Relief, if obtained, may last for two to six months but rarely longer.

**SUMMARY OF NON-SPECIFIC PROTEIN THERAPY.** Through the use of colon bacilli subcutaneously or intravenously in very small doses, non-specific protein therapy can be recommended in the treatment of general allergy if the more logical methods cannot be used for any reason or fail. Good results, if obtained, are rarely permanent. It apparently does little or no good in contact allergy and is not recommended for this.

**Symptomatic Treatment.** It does not come within the scope of this paper to discuss at length the symptomatic treatment of asthma and allied conditions for few subjects have been more thoroughly discussed in medical literature than this.

*Adrenalin.* Adrenalin is the one remedy which is relatively consistent in its effect. Other remedies, even atropine, are characterized by their inconsistency. A remedy which completely relieves one patient may have no marked influence on others. Adrenalin is also our most effective symptomatic remedy, and if properly used, will relieve the great majority of cases temporarily. The dose required varies, in fact, varies from 0.05 or 0.1 to 1 or 2 cc. In order to obtain the best effect, the dose must be adjusted to suit the individual's need. This can be accomplished usually by giving 0.25 to 0.5 cc of a 1 to 1000 solution subcutaneously at five- or ten-minute intervals until the patient experiences relief of symptoms or symptoms of reaction to adrenalin, such as nervousness, pallor, and tremor of the hands. When the amount required for relief has been determined in this way, the total amount used can be repeated, if given slowly, so often as symptoms return. In this way, continuous relief can often be obtained. After the patient has been free of symptoms for a time, the dose can often be reduced—in fact, can often be reduced gradually from a relatively large dose to a dose of 0.1 or 0.2 cc. Occasionally, however, this is not the case and larger doses have to be used and continued in order to maintain relief. Adrenalin should be repeated as soon as possible after symptoms begin to return; in fact, it is well to anticipate the return of symptoms by a few minutes if this can be done.

Adrenalin gives relief in the majority of cases of asthma. It often fails in angioneurotic edema where very large doses are frequently required. It does not give immediate relief in eczema and other illnesses where structural changes in the tissues have occurred.

Adrenalin can be used for weeks or months without serious ill effect although, perhaps, more experience is needed before the harmlessness of this drug can be relied upon if used for indefinite periods of time. I have observed several cases in which it has been used for months with apparently no serious ill effect. While adrenalin can be used continuously for months, it is best adapted for emergency treatment and temporary treatment and should

be discontinued as soon as measures which have a more lasting effect can be instituted.

*Pituitrin.* Pituitrin given subcutaneously often has an effect somewhat similar to that of adrenalin. Its immediate effect is not nearly so marked but as a rule, if the drug is effective, it gives a longer period of relief than adrenalin. It is occasionally advisable to use pituitrin and adrenalin together. Koessler warns against the use of pituitrin on account of its usually containing histamine as an impurity.

*Atropine.* Atropine in doses of  $\frac{1}{800}$  to  $\frac{1}{100}$  grain given two or three times in twenty-four hours subcutaneously or by mouth, is often valuable. It can be used in conjunction with adrenalin or it can be used alone. A dose should be used which causes dryness of the mouth but rarely a dose which causes blurred vision or dilation of the pupils. Often atropine in small doses marks the difference between success and failure in the relief of patients who have been treated according to the principals outlined earlier in the paper. A patient nearly relieved by other means often may be completely relieved with the help of atropine.

*Habit Forming Drugs.* Habit forming drugs need no detailed discussion in this paper since they are contraindicated in most chronic illnesses, especially in asthma. Emergencies which justify their use rarely occur.

**TO SUMMARIZE SYMPTOMATIC TREATMENT.** To summarize symptomatic treatment, adrenalin, pituitrin, and atropine should be looked upon as useful symptomatic remedies, best adapted, however, for temporary use while the more lasting methods of treatment are being instituted.

**General Summary and Conclusions.** The numerous manifestations of allergy, such as hay-fever, asthma, the dermatoses, the gastrointestinal, urological, and neurological symptoms, urticaria, angio-neurotic edema hypotension, etc., can be treated along five different lines, namely, avoidance or removal of the specific cause of illness, avoidance or removal of contributory causes, specific protein treatment, non-specific protein treatment, and symptomatic treatment.

Avoidance or removal of the specific cause is the method of choice when this method can be used.

Specific protein treatment is the method of choice when the specific cause of illness is known, but cannot be conveniently avoided, namely, in the case of sensitiveness to the common fall pollens and to cooked egg, milk, or wheat.

When the specific cause of illness is not known or cannot be removed or treated specifically non-specific protein treatment is worthy of trial. This can be accomplished best, I believe, through the use of colon bacilli subcutaneously or in very small doses intravenously.



Adrenalin, pituitrin, and atropine are useful symptomatic remedies well adapted for emergency use and for temporary use while the more lasting methods of treatment are being instituted.

The results of pollen therapy in the treatment of pollen hay-fever and asthma are good. The best results are obtained through the use of pollen extract subcutaneously, combined with local applications of pollen extract to the conjunctivæ and nasal mucous membrane.

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NON-SPECIFIC VERSUS SPECIFIC THERAPY IN BRONCHIAL  
ASTHMA.

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THE modern conception of anaphylaxis, as the cause of asthma, is based upon the experiments of Auér and Lewis,<sup>1</sup> who showed that bronchospasm was one of the characteristic results of anaphylactic shock in the guinea-pig. Meltzer,<sup>2</sup> impressed with the similarity of these bronchospasms to asthmatic seizures suggested that asthma was an anaphylactic phenomenon. Since then the epochal work of Walker,<sup>3</sup> and the work of Schloss,<sup>4</sup> Cooke,<sup>5</sup> Longcope,<sup>6</sup> and Rackemann,<sup>7</sup> have shown that in 40 to 50 per cent of asthmatic cases the condition is due to sensitization to food, epidermal, bacterial or pollen protein.

The specific protein therapy, following the determination by various methods of sensitiveness to proteins, is excellently carried on by Walker,<sup>3</sup> Cooke,<sup>5</sup> Schloss,<sup>4</sup> Rackemann<sup>7</sup> and others. Auto-genous vaccines from the sputum and foci of infection have also been utilized with success. Non-specific protein therapy, however, has been barely touched upon, although there is every reason to believe that even in the so-called specific protein therapy, a non-specific element plays an important part. The analogy to other fields shows this to some degree. Meyer<sup>8</sup> has pointed out that besides the specific antitoxin value of serum, in diphtheria, the horse serum protein contains a non-specific stimulating element. In the process of concentration this non-specific factor is naturally lost to a considerable degree, this fact justifying the repeatedly expressed criticism of late years, that the modern highly concentrated serum seems less effective than the old serum which was lower in antitoxic units. R. F. Vaccarezza<sup>9</sup> and his associates recently reported that in 100 cases of anthrax they found normal beef serum as effective as specific antiserum. They attributed this action to the protein element in the serum. Requiring a substance which does not sensitize, they substituted peptone and adapted it to their purpose. The results proved so satisfactory that they now use it exclusively even in septicemia.

Literature on non-specific therapy in bronchial asthma is meager. Auld<sup>10</sup> reported the use of peptone subcutaneously and intravenously. Pagniez and Widal<sup>11</sup> and Abrami and Brissaud<sup>12</sup> utilized peptone by mouth. Boyd<sup>13</sup> claimed success with intravenous injections of typhoid vaccine (50,000,000).

Impressed with the effects of autogenous vaccines in my treat-

ment of non-sensitive patients, I became doubtful as to whether I was dealing with a specific bacterial antigen, or whether the results obtained were merely the benefits of a non-specific action. This uncertainty was further strengthened by observing that recurrences after vaccine therapy could be relieved by other vaccines containing totally different organisms.

To determine the question, a preliminary test for sensitiveness to proteins was made on all patients admitted to the hospital. Approximately ninety tests were made on each patient by the cutaneous method. Cardiorenal factors and other reflex phenomena were excluded in the routine examination. Sensitive patients were divided into five groups, according to whether they had received: (1) Specific desensitization, (2) autogenous vaccines, (3) milk, (4) peptone, or (5) no treatment whatever, these last having been relieved from asthma after the offending protein was removed. The unclassified or non-sensitive patients were divided into three groups, depending on whether they had received: (1) Peptone, (2) milk or (3) autogenous vaccine.

**PREPARATION OF MATERIALS.** *Peptone.* A 33.33 per cent solution was prepared by mixing peptone, glycerin and water. The mixture of water and glycerin was added to Armour's peptone siccum (dry) slowly, rubbed well by means of a mortar and pestle, warmed gently over a water-bath with constant stirring until solution was complete, and then filtered until clear. This solution stands sterilization and will keep under any condition, no ice being necessary. The filtered preparation was then poured into a small, glass, rubber-capped vial and sterilized in an autoclave or water-bath for from thirty to forty minutes.

*Milk.* Straight whole milk was poured into a 2-ounce, rubber-capped bottle and placed in a water-bath up to the neck of the bottle and allowed to boil for one hour.

*Vaccines.* Sterile containers were furnished to patients with instructions to bring a specimen of the sputum expectorated after a severe coughing attack that is, from the deeper bronchi.

Blood-agar plates were streaked, and a loopful of the sputum was inoculated in 50 cc of 1 per cent dextrose broth, which was from 0.2 to 0.5 per cent acid. These cultures were then incubated for twenty-four hours. The blood plates were studied for the type of organism present, and a Gram stain was made of the broth culture to rule out contaminating organisms. The broth culture was then centrifuged at high speed (1500 revolutions per minute) for fifteen minutes and the supernatant broth discarded. The precipitate was washed in sterile normal salt solution and centrifuged at high speed, the bacteria being thrown down. The filtrate was suspended in 5 cc of fresh normal salt solution, put in an ampoule, and placed in a water-bath at 60° C. for one hour. This suspension was tested for sterility in dextrose broth, and then

diluted with normal salt solution so that 1 cc was equivalent to 1,000,000,000 organisms, as shown on the blood plates.

**METHOD OF ADMINISTRATION AND DOSAGE.** *Specific Therapy.* Patients sensitive to epidermal proteins were treated with commercial preparations\* supplied in dilutions of 1:100,000, 1:10,000, 1:1000 and 1:500. To determine the initial therapeutic dose, Walker's<sup>14</sup> method of testing for the degree of sensitiveness was carried out. Treatment began with 0.2 cc of the weakest solution failing to give a reaction by the dilution test. This was usually a 1:10,000 or a 1:100,000 solution. This dose was increased by 0.1 cc every five days, so that three doses of each dilution were administered, ending with six minims of a 1:500 solution.

*Autogenous Vaccines.* All vaccines were prepared so that 1 cc was equivalent to 1,000,000,000 organisms. The initial dose was 200,000,000 bacteria (3 minims), except that to sensitive patients one-half this dose was given. The dose was increased by 1 minim at triweekly intervals until 1 cc was given. This last dose was occasionally repeated two or three times at biweekly intervals.

*Peptone.* Three minims of the solution described proved a safe initial dose. This was increased by 1 minim at biweekly or triweekly intervals up to 1 cc.

*Milk.* Five-tenths to 1 cc was the initial dose administered. This was increased by 0.5 to 1 cc at triweekly intervals up to 3 cc, which dose was never exceeded. In some cases the 2-cc dose was never exceeded.

*Comment.* Experience alone can enable one to decide the dosage, which must be determined according to the symptoms and progress in the case. In the event of a severe local reaction with any of the above preparations, the preceding dose should be repeated. Early recognition of the approach to the limit of tolerance is important. The first symptoms are nausea with vaccine; drowsiness and chilliness with peptone; epistaxis and bilateral frontal headaches with milk. (Epistaxis, in which a few drops of blood were lost three or four times a day, for one or two days, occurred in 3 cases.) If any of these symptoms arise during the treatment, it is advisable to repeat the last dose and thereafter increase cautiously approximately one-half the usual increase.

TABLE I.—EFFECT OF PROTEIN THERAPY ON SENSITIVE PATIENTS.

Treatment.	No. of patients.	Relieved of asthma.	Markedly improved.	Unimproved.
Milk . . . . .	10	4 ( 40.0 per cent)	5 (50.0 per cent)	1 (10.0 per cent)
Peptone . . . . .	3	2 ( 66.6 " )	0	1 (33.3 " )
Vaccine (autogenous)	14	5 ( 35.7 " )	6 (42.9 " )	3 (21.4 " )
Specific therapy . .	11	5 ( 45.4 " )	3 (27.3 " )	3 (27.3 " )
Omission . . . . .	7	7 (100.0 " )	0	0

\* Arlington Chemical Company's products used exclusively.

Of the 10 sensitive patients on milk therapy none gave a hereditary history. Three were positive to epidermal and food proteins; 4 to epidermal; 1 to food and pollen; 1 to food; 1 to pollen. Two were changed from vaccine and relieved of asthma; 1 was changed from peptone and markedly improved; 1 was changed to vaccine with no improvement. Eight were males, and 2 were females; ages eighteen to fifty-six years. The duration of the disease was two to forty-nine years. One was changed from specific therapy and markedly improved.

Of the 3 sensitive patients on peptone therapy, none gave a hereditary history. All patients were positive to an epidermal protein. One was changed from vaccine and relieved of asthma; 1 was changed to milk and markedly improved. Two were males, and 1 was a female; ages forty to fifty-four years. The duration of the disease was eight to fourteen years.

Of the 14 sensitive patients on autogenous vaccine therapy, 3 gave a hereditary history. Six were positive to an epidermal protein; 2 to food; 2 to pollen; 2 to bacteria; 1 to epidermal protein and food; 1 to pollen and food. Two were changed to milk and relieved of asthma; 1 was changed from milk and unimproved; 1 was changed to peptone and relieved of asthma. Nine were males and 6 were females; ages, fourteen to forty-nine years. The duration of the disease was one to thirty years.

Of the 7 sensitive patients to whom no treatment was given, 2 gave a hereditary history. Six were positive to epidermal proteins and 1 to food. Four were males and 3 were females; ages, twenty-one to forty-eight years. The duration of the disease was one month to twenty-nine years.

TABLE II.—EFFECT OF PROTEIN THERAPY ON NON-SENSITIVE OR UNCLASSIFIED PATIENTS.

Treatment.	No. of patients.	Relieved of asthma.	Markedly improved.	Unimproved.
Milk . . . . .	8	6 (75.0 per cent)	1 (12.5 per cent)	1 (12.5 per cent)
Peptone . . . . .	8	5 (62.5 " )	3 (37.5 " )	0
Vaccine (autogenous)	43	20 (46.4 " )	20 (46.4 " )	3 ( 7.2 " )

Of the 8 non-sensitive patients on milk therapy, 3 gave a hereditary history. Four were males and 4 were females; ages, twenty-five to fifty-nine years. The duration of the disease was four months to thirty-nine years.

Of the 8 non-sensitive patients on peptone therapy, 1 gave a hereditary history. Four were males and 4 were females; ages, fourteen to fifty-one years. The duration of disease was five weeks to twelve years. One was changed from vaccine and relieved of asthma.

Of the 43 patients on autogenous vaccine therapy, 15 gave a hereditary history. Twenty were males and 23 were females; ages, ten to seventy years. The duration of the disease was four months to forty-four years. One was changed to peptone and relieved of asthma.

**Report of Cases.**—**CASE I.**—**E. U.**, a man, aged thirty-eight years, entered the hospital, August 24, 1922, complaining of having had for two years continual attacks of asthma with paroxysmal coughing and dyspnea between 2 A.M. and 5 A.M. and attacks of coughing during the day. He had pneumonia and empyema with thoracotomy when nine years of age, and had frequent attacks of bronchitis thereafter. Physical examination of the chest revealed emphysema and bronchitis, and a thickened pleura on the right side beneath the ninth rib (below the scar of his previous operation). The roentgenological examination verified this finding, and showed a considerable elevation of the right diaphragm (pleuro-diaphragmatic adhesions) and a generalized thickening of the bronchial wall, with accentuation of the pulmonic markings, especially the right lower lobe. Cultures of the sputum were made and a hemolytic streptococcus as well as a staphylococcus was recovered. The urine and Wassermann tests were negative. The cutaneous tests showed a positive reaction with the pollen (corn).

On September 19 he received 1 cc of milk, injected subcutaneously. On September 21 and thereafter at weekly intervals 2 cc were injected. On October 26 and 31, 3 cc were injected.

*Comment.* Following the second injection, the paroxysmal dyspnea ceased and the patient had but one paroxysmal attack, on October 26. Since his discharge on October 31 an occasional cough has been the only symptom. Examination of the chest, January 17, 1923, showed emphysema, thickened pleura, right base and only an occasional rale.

**CASE II.**—**M. W.**, a woman, aged twenty-five years, entered the hospital, December 22, 1922, complaining of having had asthma for the preceding two or three years, the attacks lasting from seven to ten days, the longest free interval being two weeks. After violent coughing she expelled some sputum mucopurulent in character.

Physical examination of the chest revealed emphysema with marked bronchitis. Cultures of the sputum were made and a *Staphylococcus aureus* was recovered. The urine and chemical blood examinations were normal, and the Wassermann negative. The cutaneous tests showed a 1+ reaction to cat hair and lobster.

She received six injections of milk, subcutaneously, beginning with 0.5 cc up to 3 cc, at biweekly intervals, ending January

30, 1923. Following the second injection she was relieved of asthma.

*Comment.* This patient had not changed her daily routine, for she was not informed of her sensitiveness to cat hair and lobster until February 6, 1923, when she reported that she was still free from all symptoms.

CASE III.—F. H., a man, aged fifty-two years, entered the hospital, November 9, 1922, complaining of having had asthma for forty-nine years, the attacks being continual all the year round, lasting two hours or more, with coughing, wheezing and expectoration between paroxysms. He had some expectoration of thin gray sputum.

Physical examination of the chest revealed emphysema and typical music-box findings. The patient also had chronic myocarditis and a right inguinal hernia. He had received treatment at one of the New York asthma clinics for one year without results. Cultures of the sputum were made and a pneumococcus, a hemolytic streptococcus and a green streptococcus were recovered, from which a vaccine was prepared. The Wassermann and urine examinations were negative and the cutaneous tests revealed a 2+ reaction to wool.

On January 11, 1923, he received 7 minims of adrenalin chloride (1:1000) for the relief of an acute attack. On January 16, 3 minims of his autogenous vaccine were injected. On January 18 and 20, 4 and 5 minims, respectively, were injected, followed by an aggravation of his symptoms. On January 23 his treatment was changed to milk injections. He has now received six injections at biweekly intervals and is markedly improved. He still has short attacks, mild in character, lasting half an hour, but his sleep is now practically undisturbed. He showed a good local reaction after each injection, but no constitutional symptoms.

CASE IV.—A. R., a man, aged fifty-six years, entered the hospital, December 30, 1922, complaining of having had asthma for eleven years, the attacks lasting from five to seven days, the longest free interval being one week. Coughing between attacks was constant. The burning of asthma powder gave relief.

Physical examination of the chest revealed emphysema with bronchitis. He also had a high-grade pyorrhea, an enteroptosis, and a right inguinal hernia. The heart sounds were of poor muscular quality.

The cutaneous tests showed a 1+ reaction to tomatoes and coffee.

He received six injections of milk, beginning with 1 cc and gradually increasing to 3 cc, at biweekly intervals; with an absence of paroxysms since the initial injection, January 23, 1923. On February 15 he reported himself free from attacks.



CASE V.—A. B., a man, aged forty years, entered the hospital, September, 1921, complaining of having had asthma for ten years, the attacks being continual but severest during the winter months, lasting about a month, with the longest free interval of two weeks. He gave a history of syphilis of four years' duration.

Physical examination of the chest revealed emphysema with bronchitis. The Wassermann showed a 3+ reaction. The cutaneous tests showed a 2+ reaction to rabbit hair.

Desensitization was instituted and he was discharged in December, 1921, relieved of asthma. He returned December 14, 1922, complaining of having had attacks of asthma for the preceding three weeks. These attacks were so severe that he was confined to his home for that period. On physical examination the findings were identical with those on the first admission. The cutaneous tests showed a 2+ reaction to goose feathers and a negative reaction with rabbit hair. He received nine injections of milk, beginning with 1 cc, December 21, 1922, and gradually increasing up to 2.5 cc at biweekly and triweekly intervals. Following his second injection he was free from asthma. On February 8 he reported that he was entirely free from symptoms.

*Comment.* This patient, originally sensitive to rabbit hair, was entirely free for about one year following specific desensitization. On readmission the cutaneous tests showed that he was then sensitive to a different epidermal protein—goose feathers. He is now entirely free from symptoms following non-specific therapy—milk. Syphilis apparently played no part in this picture for he had received no antisyphilitic treatment at any time.

CASE VI.—A. D., a man, aged fifty-four years, entered the hospital, September 27, 1922, complaining of having had asthma since 1911, the attacks occurring all the year 'round and being worse during the summer months.

Physical examination of the chest revealed emphysema with typical music-box findings. He also had a marked pyorrhea and a high-grade enteroptosis. The red blood count was 4,328,000; white blood count, 17,800; polymorphonuclear cells, 17 per cent; lymphocytes, 13 per cent; eosinophils, 4 per cent; transitional, 5 per cent; mononuclear, 8 per cent; small lymphocytes, 9 per cent; large lymphocytes, 4 per cent; red cells, negative. The cutaneous tests revealed a 1+ reaction to chicken feathers and a = reaction to ragweed short and ragweed giant.

On November 2, 1922, he received 3 minims of peptone subcutaneously. This dose was increased by 1 minim at weekly intervals for six doses with no improvement. There was no local reaction following any of the injections. On December 19, 1 cc of milk was injected subcutaneously and thereafter at weekly intervals 2.5 cc were injected for five doses. He had one attack

on January 13, lasting two hours, following the fourth dose. A good local reaction followed each injection.

*Comments.* This patient, sensitive to an epidermal protein and possibly to a pollen protein, did not respond favorably to peptone. Following the first injection of milk, the paroxysms ceased and he has had but one mild attack since. On February 8, a slight cough was the only remaining symptom.

CASE VII.—R. S., a woman, aged fifty-nine years, entered the hospital, November 22, 1922, complaining of having had asthma since April, 1922, the attacks having come on every night with no free intervals, beginning usually at 3 A.M. and associated with dyspnea, paroxysmal coughing and inability to lie in the prone position. The attacks were becoming progressively more severe. She complained of frequent colds prior to the onset of asthma. The chemical blood examination on November 6 showed: Sugar, 0.08 mg.; urea nitrogen, 16.9 mg.; chlorides, as NaCl, 0.5 mg. per 100 cc. The urine and Wassermann examinations were negative.

Physical examination of the chest revealed emphysema with sibilant and sonorous rales throughout. There was a marked enteroptosis and stigmas of ovarian insufficiency. The heart showed an accentuation of the aortic sound; the blood-pressure was 220/120; the cutaneous tests were negative.

Four doses of milk were injected subcutaneously, beginning with 1 cc on January 16; on the 18th, 1.5 cc; on the 23d, 2 cc; on the 30th, 2.5 cc. Following the second dose only a slight cough remained, which did not disturb sleep. On February 13 she was still free from attacks. The blood-pressure on February 6 was 240/120. The chemical blood on February 12 showed: Sugar, 0.14 mg.; urea nitrogen, 13.4 mg.; chloride, as NaCl, 0.5 mg. per 100 cc.

*Comment.* This case is of interest because of the rather late onset of symptoms, and it also shows that hypertension, in itself, has no bearing on the paroxysms in such a case. The hypertension undoubtedly is part of the menopausal syndrome.

CASE VIII.—R. S., a boy, aged fourteen years, entered the hospital, July 25, 1922, complaining of having had asthma for the past eight years, the attacks being continual, lasting from one to three days, the longest free interval being one week. The urine and cutaneous tests were negative.

Physical examination of the chest revealed emphysema and bronchitis.

Three minims of peptone were injected subcutaneously on August 12. This dose was increased by 1 minim every three, five or seven days; the last seven at weekly intervals, reaching 1 cc on December 16. The 1-cc dose was repeated on December 23,

followed by a one-hour attack, which was the first in five weeks. He reported short attacks on December 27, 28 and 29. Seven minims were injected on December 30, this dose being increased by 1 minim at weekly intervals, reaching 10 minims, January 27, 1923. He has been entirely free from symptoms since December 29, 1922. On February 13 he reported freedom from symptoms, with a gain of 2 pounds over the preceding week.

*Comment.* During the months that this boy was under treatment he had four short attacks, caused probably by the large doses of peptone administered, which indicates that excessively large doses are not tolerated.

CASE IX.—M. P., a woman, aged forty-one years, entered the hospital, November 9, 1922, complaining of having had asthma since September, 1921, the attacks occurring only during the winter months, lasting one to two weeks, with the longest free interval of two weeks. Between the paroxysmal attacks she had wheezing, coughing and a feeling of tightness in the chest. The urine and Wassermann examinations were negative, and the cutaneous tests showed a  $\pm$  reaction to duck feathers.

Physical examination of the chest revealed emphysema, with a moderate number of whistling rales at the bases with muffled breath sounds.

On December 12, 1922, 3 minims of peptone were injected. On December 16 she reported having had two severe attacks. Four minims were injected. On December 19 she reported freedom from attacks. She then received 6 minims on December 21, 7 on December 26 and 8 on December 30. January 9 she reported having had a twenty-minute attack following her entrance into a freshly painted room. Eight minims were injected on January 9, with an increase of 1 minim every three days thereafter, reaching 13 minims, January 24, 1923. During this entire time she was without any attack except as noted above. Her last report on February 13 showed that she was still free from attacks.

CASE X.—E. L., a man, aged forty years, entered the hospital, November 17, 1921, complaining of having had asthma for the past fourteen years, the attacks lasting from one to four weeks, the worst period being August to September or continuing on through the winter until May. He also had sneezing, itching of the eyes and lachrimation during the summer months. The sputum was tenacious, the predominating organism being a diplococcus. A few pus cells were present. The cutaneous tests showed a 2+ reaction to dog hair, chicken feathers and sheep wool.

Physical examinations of the chest revealed emphysema and typical music-box findings.

On July 13, 3 minims of peptone were injected subcutaneously.

This dose was increased by 1 minim at biweekly and triweekly intervals until 1 cc was given on August 3. He suffered no attacks following his first injection on July 13. On February 6, 1923 he reported himself still free from attacks.

CASE XI.—R. L., a woman, aged fifty years, entered the hospital, May 23, 1922, complaining of having had asthma for the last eight years, following an attack of bronchitis, the attacks occurring at weekly intervals and lasting about a week. The urine examination was negative. Cultures of the sputum revealed the presence of a hemolytic streptococcus and a pneumococcus, from which a vaccine was made. The cutaneous tests showed a positive reaction to goose feathers.

Physical examination of the chest revealed emphysema. On auscultation the chest was a veritable music box.

June 27, 1922, 3 minims of the vaccine were injected subcutaneously. This dose was increased by 1 minim at biweekly and triweekly intervals to 1 cc, which was reached on July 29, this dose being held for four additional injections to August 17, at which time she reported that she had had no attacks for a period of three weeks. She returned on October 7, with a recurrence, having had attacks for the preceding ten days. Three minims of peptone were injected subcutaneously on that day; on October 10, 4 minims; on October 17, 5 minims; on October 22, 6 minims; she reported no attacks since October 10. She returned on December 7 entirely free from attacks, but had contracted a cold and had a severe cough. A simple expectorant and salicylates were prescribed with benefit. On February 8, she again reported having contracted a cold associated with cough. The same medication was prescribed with relief.

CASE XII.—F. M., a man, aged thirty-nine years, entered the hospital, March 15, 1921, complaining of having had asthma for twenty-nine years, the attacks usually beginning with stomach symptoms, belching of gas or burning sensation in the abdomen, followed by a sense of oppression in the chest, dyspnea and cyanosis, with a feeling of impending death. He had some expectoration of a gelatin-like phlegm. He was always worse on Sunday and believed that tub-bathing aggravated his condition. The attacks would occur continually and would last five days a week. There was a definite hereditary history of asthma. The Wassermann and urine examinations were negative. The sputum was a grayish fluid, with a staphylococcus predominating. The red blood count was 4,272,000; the white blood count, 10,400; the hemoglobin was 80 to 90 per cent (Talquist); polymorphonuclears, 58 per cent; neutrophils, 51 per cent; eosinophils, 6 per cent; basophils, 1 per cent; transitionals, 4 per cent; large mononuclears, 2

per cent; lymphocytes, 35 per cent (18 large and 17 small). The cutaneous tests showed a 4+ reaction to rabbit hair and a  $\pm$  reaction to dog hair.

Physical examination of the chest revealed emphysema with bronchitis. An enteroptosis and a hydrocele of the left cord about 2 inches in diameter were also present. Further questioning disclosed the fact that the patient had had rabbits in his home for the preceding nine years. Following the removal of the rabbits, with the scrubbing up of the bathroom where these rabbits were housed, and the boiling of all linen there immediately followed complete freedom from attacks. February 7, 1923, he reported himself still free from attacks and that he had not lost a day of work, due to illness, since his discharge, March 17, 1921.

*Comment.* This man, brought up on a farm, was undoubtedly sensitized to an epidermal protein at the age of ten years, probably that of dog hair. On coming to the city he brought some pet rabbits with him, replacing them from time to time with new ones, thus keeping up his sensitized state. The fact that he was worse on Sunday and that his symptoms were aggravated by tub-bathing was due to the more intimate contact with the offending protein. Regardless of the presence of the various foci of infection he has been entirely free from symptoms since the removal of the rabbits.

CASE XIII.—C. T., a woman, aged twenty-nine years, entered the hospital, April 12, 1921, complaining of having had asthma since September, 1920, the attacks occurring about midnight of every third night and lasting until noon of the following day. She had left for Ohio in October and had no attacks during her stay. She returned to her home on December 8 and the attacks returned on December 21, then recurring every third night as before. There was a history of asthma in the family.

Physical examination of the chest revealed emphysema with bronchitis. A seven months' pregnancy was also present.

The cutaneous tests showed a  $\pm$  reaction with horse dander. By persistent questioning, suspicion was directed toward a rag rug, presented to her as a wedding gift, three weeks prior to her onset of asthma. She was instructed to remove this rug from her home. Returning in two weeks, she reported no attacks in that interval. She was then requested to replace the rug in her home with the result that her attacks returned with the same periodicity. A specimen of this rug was examined, revealing the presence of horse hair. With the permanent removal of the rug she was entirely free from asthmatic seizures until March, 1922. An attack of moderate severity immediately followed a known exposure to horses. Specific desensitization was then instituted, and was completed on June 22.

*Comment.* The importance of an erythema alone is clearly shown as well as the necessity of diligent search for the possible location of the protein involved. The definite periodicity of the attacks suggests that epidermal proteins have an accumulative action.

COMPARATIVE RESULTS WITH SPECIFIC AND NON-SPECIFIC THERAPY IN CASES OF SENSITIVENESS. A critical analysis of Table I with special reference to the results obtained by the various methods used is my strongest evidence at present in favor of non-specific therapy in the treatment of asthma more or less as a routine measure, except in cases of sensitiveness where the removal of the offending protein is followed by relief of asthma. It is clearly demonstrated that the best results are obtained when symptoms of asthma are relieved after the removal of the offending protein. These cases may continue indefinitely without symptoms, as shown by Cases XII and XIII, which fact is indisputable evidence of the specificity of the skin tests. Peptone evidently shows a higher percentage for cases of relief of asthma; autogenous vaccine and milk, a somewhat lower percentage than specific desensitization. But milk and vaccine show a higher percentage of cases of marked improvement than does specific therapy. The percentage of patients unimproved was somewhat higher with specific therapy than with vaccines or milk but lower than with peptone.

The results obtained with milk and peptone indicate distinctly that a non-specific element plays an important part in the desensitization. This deduction is further strengthened by the fact that a large percentage of cases show a positive skin reaction with the original protein after specific desensitization, where the patients were free from all symptoms for a considerable period of time. This phase of the study will be discussed in a subsequent report.

NON-SPECIFIC AGENTS *vs.* AUTOGENOUS VACCINES IN CASES OF NON-SENSITIVENESS. In comparing the results obtained with the use of milk and peptone as against autogenous vaccine, shown in Table II, one cannot help but note the marked difference between them. Walker, reporting a series of 75 non-sensitive patients treated with autogenous vaccines, showed 46.6 per cent relieved of asthma and 16 per cent improved. The results obtained in this series compare favorably, 46.4 per cent being relieved of asthma and 46.4 per cent markedly improved. Milk showed 75 per cent relieved of asthma and 12.5 per cent markedly improved; peptone, 62.5 per cent relieved of asthma and 27.5 per cent improved.

Auld,<sup>10</sup> using peptone intravenously and subcutaneously, observed that his cases could be divided into two main groups, showing no tendency to pass into each other. One group comprises patients who quickly respond to the treatment and in whom recurrences are less frequent and milder in character. The other group

is composed of resistant patients and is subdivisible into groups of totally resistant patients and those in whom, by careful immunization, the disease may be largely overcome. A similar experience was noted in this series. Some patients responded almost immediately, usually after the second or third dose, as shown by Cases IX and X; others needed prolonged treatment, such as the patient in Case VIII, and some were resistant to continued treatment, such as those in Case VI. The exact observation was made with milk. However, patients failing to respond to milk, quickly respond to peptone and *vice versa* and others were resistant to both. This observation rather depreciates Peterson's<sup>15</sup> statement that peptone seems to be polyvalent for most of the substances causing anaphylaxis.

In comparison vaccines act in the same manner. When one fails a new vaccine obtained from the same source, but containing different organisms, will prove successful. Walker<sup>16</sup> attributes this fact to the isolation of the specific causal organisms. Some doubt is cast upon this interpretation, for the same phenomenon is noted with a change of non-specific agents. The explanation for this difference in the response to the various proteins can best be interpreted on the basis of Weichardt's<sup>17</sup> theory of "omnicellular plasma-activation."

The important factor in the use of non-specific proteins as a routine measure is the avoidance of anaphylaxis. This may be accomplished by testing for sensitiveness with the cutaneous test similar to the tests for sensitization. Properly carried out, this test should do away with the objection raised against the routine use of non-specific proteins.

**Summary.** 1. The cutaneous tests are undeniably specific and should be carried out in every case, for, as has been shown, where symptoms cease upon removal of the offending protein the best results are obtained.

2. A non-specific element enters largely into the benefits derived from specific desensitization.

3. The judicious use of non-specific proteins is a valuable adjunct to the treatment of bronchial asthma and should be used more or less as a routine procedure.

4. Milk is the non-specific agent of choice because of its ready supply and ease of preparation.

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## THE DURATION AND MAGNITUDE OF THE HYPOGLYCEMIA AFTER INSULIN.

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It has been recognized since the first published work of Banting and his collaborators<sup>1</sup> that the effect of insulin was of rather short duration. Recent work has shown<sup>2</sup> that in rabbits the extent of the reduction in the blood sugar does not follow closely the dose per kilo of body weight nor does it correspond to the actual level of blood sugar before the injection is made. The effect of a large dose of insulin is said to give a more prolonged reduction of the blood sugar than a smaller one, but the extent of reduction is not so much greater in the case of the larger dose as might be expected. In treating cases of diabetes with insulin it early became evident that we could not predict with any accuracy the amount of the



drug to be used in a given case to secure a definite reduction in the blood sugar level. The frequency of dosage necessary to keep diabetics without glycosuria was evidently variable. These clinical studies will be presented separately in a later paper. It is our purpose here to present studies of the effect of insulin on the blood sugar concentration of normal adults.

The subjects of these experiments were healthy students or members of the medical staff. The insulin used was in all cases "Iletin," supplied by Eli Lilly Company, whose coöperation is gratefully acknowledged. The dosage was in terms of the "unit" as marked on the vials of the drug. "The unit of Iletin originally adopted was the amount required to lower the normal blood sugar of a 1 kilogram rabbit to 0.045 per cent." The dose was given as a single subcutaneous injection into the arm. Blood samples were taken from the antecubital veins, oxalated, and analyses begun at once by the method of Folin and Wu. During the period when blood samples were being taken the subjects were engaged in sedentary laboratory work, attending lectures, or passing from one room to another in the same building. None of the subjects had any food between the previous evening meal and the time of the last blood sample. The experiments were begun between 8 and 9 A.M. Four individuals were given 4 units each of insulin, Nos. 1, 2, 3 and 4. To Nos. 5 and 6 were given 8 units, and to Nos. 7 and 8 the maximum of 10 units. Fig. 1 shows the changes in the blood sugar level in these cases. The same sample of insulin was used for all these cases except No. 7. In the latter case a portion was used from a second lot of the drug of the same strength. The curves are marked with the body weights of the subjects in kilos. The intervals designated by S in the curves for Nos. 7 and 8 indicate the period during which there were symptoms referable to the insulin. In both cases symptoms began almost suddenly a few minutes after the second blood sample had been taken. In the first case symptoms were not expected. In the second the subject was skeptical as to the basis of the symptoms in the first case, but experienced very similar sensations. Both these subjects were members of the medical staff, and were accustomed to taking blood samples from each other in the fashion used here. Neither one feared in the least the consequences of a slight overdose, since they were familiar with the usual means of relief from such emergencies. There seems consequently little possibility of a psychic factor. The symptoms noted were a sense of trembling and poor muscle control. There was a feeling of weakness or exhaustion. The trembling was manifested by a slight, coarse tremor, but more particularly by inability to write a normal hand or to use a slide rule. There was no blurring of vision and no sweating. These symptoms were diminishing definitely in the second hour, and had disappeared entirely by the end of the third hour.

It is evident from the curves of Nos. 1 to 4 that the magnitude of the reduction of the blood sugar level is not the same in all cases. Neither does the effect seem parallel to the dose per unit of body weight. The blood sugar concentrations in cases 1, 2 and 4 were close before giving the insulin, *i.e.*, 79, 85 and 84 mg. per 100 cc. In the samples of blood drawn from one to one and one-half hours

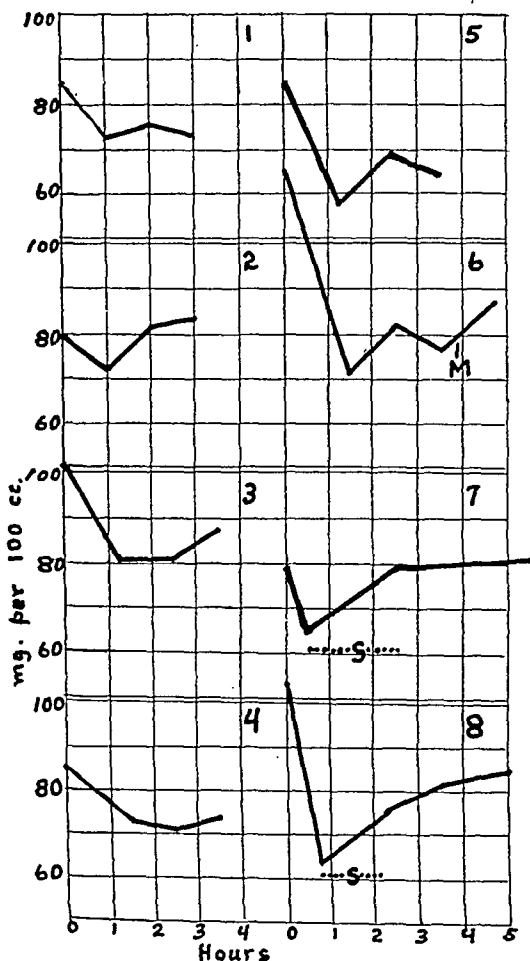


FIG. 1.—Blood sugar after injection of insulin.

4 UNITS EACH.			8 UNITS EACH.			10 UNITS EACH.		
1	.	59Kg	5	.	76Kg	7	.	82Kg
2	.	65Kg	6	.	63Kg	8	.	66Kg
3	.	68Kg						
4	.	74Kg						

after the injection, the values were strikingly close, 72, 73 and 72 mg.; but in No. 3 the initial level was higher, 101 mg., and the level was 80 mg. one and one-quarter hours later. This is a greater drop actually and relatively. Neither the actual decrease, the percentage decrease, nor the final blood sugar level seems uniform, nor related exactly to the dose per kilo.

The duration of the hypoglycemia is likewise variable. In No. 2 the original value is restored in two hours, in Nos. 1 and 4 the low levels are maintained at least three hours. In No. 3 the return to a normal level is not evident until after two and one-half hours. Both the smallest and the largest subject in the series show the slowest return toward a normal level.

In the 2 cases Nos. 5 and 6, where 8 units of insulin were the dose, the drop in blood sugar is from 84 mg. to 58 mg. and from 115 mg. to 70 mg. The subject with the greater body weight has the smaller change, but the variation is not proportional to body weights. The initial blood sugar value in No. 6 is higher than is usually found in normal adults, but there was no evident reason for this level. The return toward a normal blood sugar level is not shown completely by these curves, but it is evident that the process is not complete at the end of three and one-half hours. Subject No. 6 had a moderate noon meal beginning at the point indicated by "M" in the curve. The blood sugar about one-half hour after the meal had not risen above an average fasting level. There is apparently a rather rapid rise in the blood sugar after the minimum value has been reached, followed by a slower continued rise to the normal value.

The curve of No. 8 shows this delayed return to the normal level continuing for some time after the symptoms had abated. Both subjects 7 and 8 received the same dose, had the same blood sugar level just before symptoms began to appear, 65 and 64 mg. per 100 cc, and had symptoms for about the same length of time. The body weights varied widely and the initial blood sugar levels were 79 and 104 mg.

It seems impossible therefore to relate in any exact way the total dose or the dose per kilo to the actual or relative magnitude of the decrease produced in the blood sugar level. Nor can it be said that symptoms will appear at a definite blood sugar concentration. No. 5 went as low as 58 mg. per 100 cc with absolutely no symptoms, although Nos. 7 and 8 experienced trembling and weakness at a higher level. The duration of the hypoglycemia is likewise variable. Probably the larger doses cause a more lasting effect, but recovery is complete in No. 7 in two and one-half hours following 10 units, whereas it is incomplete in Nos. 1 and 4 after a longer period, although only 4 units had been injected. The impression from these curves is that the larger doses give greater reductions in blood sugar, tend to cause more prolonged effects, and that body weight has relatively a slight influence. These statements should be compared with the conclusions based on observations on insulin given to rabbits:<sup>2</sup> ". . . There is no contrast in the immediate results following injection of 0.3 and of 0.6 cc of the same preparation of insulin, which would indicate that so far as the initial rate of decline of blood sugar is concerned

a moderate dose has the same effect as an excessive one. The point of distinction between the moderate and excessive doses is more particularly with regard to the duration of their action." It is our impression that the extent of the decline of blood sugar is more striking than the duration of this reduced level. The curves shown in the article<sup>2</sup> referred to do not agree with the interpretation given. Both are admittedly variable, and are not subject to prediction.

Further evidence of the variable effect of insulin in the human body is presented in the study of the effect of the extract on the glucose tolerance curves of a number of normal subjects. These individuals were students who came to the laboratory without breakfast. A blood sample was taken, the dose of insulin given, and 100 gm. glucose given, dissolved in 200 cc water flavored with the juice of one lemon. Blood samples were taken at intervals during the morning, and urine samples were collected for the periods between the blood samples. The sugar content of the urine samples was determined by the method of Folin and Berglund.<sup>3</sup> During the period covered by the blood samples the subjects remained in the laboratory, seated most of the time. In some cases there was a slight sense of gastric distress, which was often relieved by drinking water about half an hour after the glucose was given. In each case a normal tolerance curve was determined on one day, and two or three days later the experiment was repeated with the use of insulin as indicated. The results are shown graphically in Figs. 2 and 3. If the normal curves are compared with each other, it is evident that there is no correlation between the body weight and the effect of 100 gm. of glucose. This corresponds to from 1.4 to 2.0 gm. per kilo body weight. But the three individuals whose tolerance curves are lowest, Nos. 13, 14 and 15, received 1.92, 1.90 and 1.67 gm. per kilo. The three whose curves extend the highest, Nos. 12, 17 and 19, received 1.43, 1.67 and 1.56 gm. per kilo. All these individuals must be considered normal. In no case did the urine sugar concentration reach 0.1 per cent, the concentration at which the clinical qualitative tests would have detected it. The highest points in these normal curves are in every case at either the half hour or one hour period after the ingestion of the sugar. Only within wide limits can the tolerance test be said to depend on the amount of sugar ingested per kilo weight. Besides the rate of absorption from the intestine, the nutritional state of the body with regard to glycogen must be an important factor. The body mechanism for the conversion of food glucose into the forms of carbohydrate which are used or stored in the body appears to operate better after a second portion of sugar than after the first ingested a very few hours previously.<sup>4</sup> Recent work<sup>5</sup> suggests that this mechanism may be the conversion of the alpha and beta glucose which is absorbed into the gamma form

for use in the oxidative and glycolytic functions of the body. This transformation is thought to be brought about by the liver and the pancreas together. The rate at which such a mechanism would become active at its optimum rate may well vary as do many other visceral functions even in the normal body. With so many variable factors it is too much to expect that an artificial condition

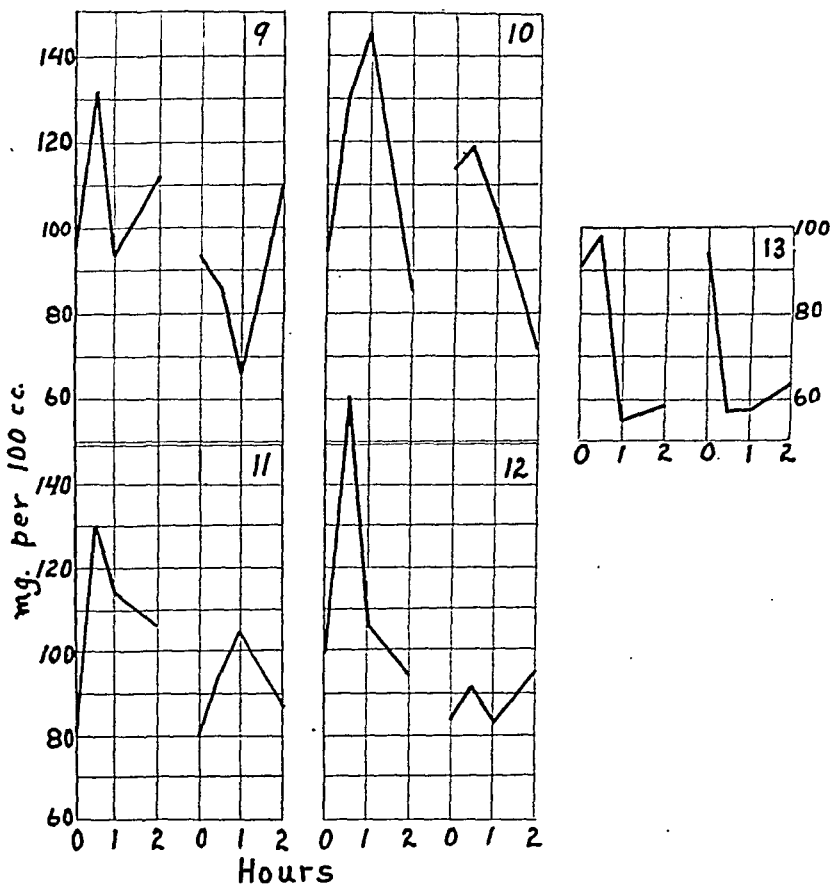


FIG. 2.—Glucose tolerance before and after insulin injection.

8 UNITS EACH.

9 . . . . .	54Kg
10 . . . . .	61Kg
11 . . . . .	70Kg
12 . . . . .	70Kg
13 . . . . .	60Kg

such as the feeding of 100 gm. of glucose would be followed by a uniform response in different individuals.

If now the tolerance curves after the administration of the insulin are compared with the normals, ten of the eleven individuals show a definitely lower curve due to the insulin. The extract is responsible for facilitating the removal from the blood of the

sugar being absorbed. But when the different curves are compared, as for example those of Nos. 9 to 13, all of which are from

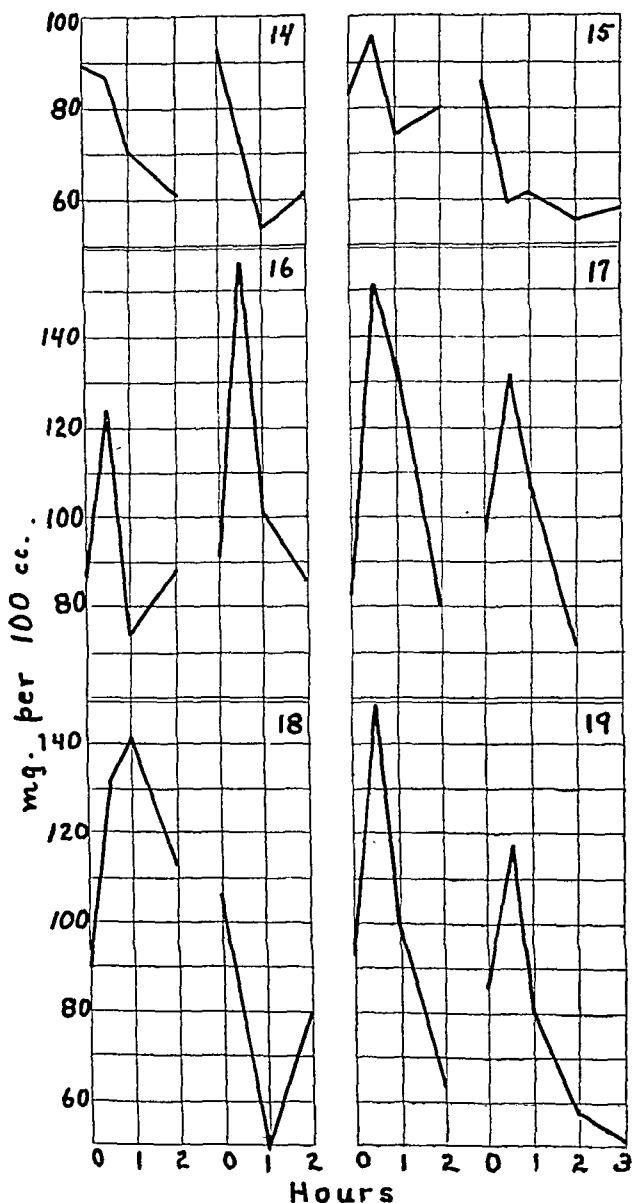


FIG. 3.—Glucose tolerance before and after insulin injection.

10 UNITS.		12 UNITS.		16 UNITS EACH.	
14 . . . . .	52Kg	15 . . . . .	53Kg	16 . . . . .	51Kg
				17 . . . . .	60Kg
				18 . . . . .	60Kg
				19 . . . . .	64Kg

subjects treated just alike, with 8 units of insulin, there is no constancy to the shape of the curve, to the maximum or minimum, and no constant relation to the curve from the same individual

without the use of insulin. The same may be said of Nos. 16 to 19, where 16 units was the dose. The tolerance test is not a physiological constant although it may be of real value in clinical diagnosis.

These tolerance test curves were not constructed to determine the duration of the effect of insulin, but some interesting observations were made in the cases of Nos. 16, 18 and 19. These three individuals, having received 16 units of insulin each, were under observation for the two-hour period represented by the curves. Since in no case so far had any symptoms of overdosage been observed they were allowed to return to classes. They reported later that just about four hours after the injection of the insulin, or two hours after leaving the laboratory, they had become very weak and faint. These symptoms had come on during or immediately after the noon meal, and were consequently of only short duration. From the concentration of the blood sugar in No. 19, 52 mg. per 100 cc three hours after injection, this is not surprising. But there is no more reason, *judging from the curves for the two-hour period*, to expect a reaction in Nos. 3, 16 and 18 than in Nos. 10, 13, 14, and 15. The conclusion which seems quite evident is that the insulin persisted in its effects for more than four hours from the time of injection, in spite of the fact that a "meal" of 100 gm. of glucose had been given immediately after it. If these curves had been continued to cover a period of five or six hours, they would probably show a more pronounced hypoglycemia in the later hours.

It is regrettable that we have no determinations of the blood sugar concentration during the period of symptoms in these cases. However it is of interest to note that in subject No. 18 a value of 49 mg. per 100 cc and in No. 19 of 52 mg. per 100 cc was reached *without* any symptoms. In subjects Nos. 7 and 8 the symptoms came on just after the blood sugar had dropped to 65 and 64 mg. per 100 cc. This is probably due to the rapid rate of decline in blood sugar level in the latter cases as compared with those where the decline came after the 100 gm. of glucose had been utilized. With such a rapid rate of decline it is probable that the curves as shown for Nos. 7 and 8 do not show the true minima. These values may be below 50 mg. per 100 cc. It is our feeling however that the reason for the variation in the level of blood sugar at which the first symptoms of overdosage become evident is an individual variation. We have observed in two diabetic men under treatment that when symptoms were observed the blood sugar concentration was between 60 mg. and 65 mg. per 100 cc in the one, and between 40 mg. and 50 mg. per 100 cc in the other. This was confirmed three times in 1 case and twice in the other.

The tolerance curves, both normal and after insulin, of Nos. 13, 14 and 15, are of different shape from the usual curve. The

absence of a significant rise of blood sugar after the ingestion of the glucose might be explained by a failure of the glucose to pass through the stomach.<sup>6</sup> But these curves show very definite declines one and two hours after the ingestion of the glucose. This hypoglycemia following a meal is as characteristic as the hyperglycemia on which attention is more usually focussed.<sup>7</sup> After the use of insulin in these 3 cases the change is that the hypoglycemia comes more rapidly and the slight peak which occurred in 2 of the curves before is now absent in all. May it be that these are individuals in which the mechanism for metabolizing glucose is so quickly and easily activated by glucose that venous blood never has a hyperglycemia after the ingestion of such a "meal"? Insulin seems to facilitate this process somewhat. These three individuals might be thought of as having unusually active pancreatic glands. Nos. 14 and 15 are sisters.

We have not added to the curves the urine sugar concentrations. In some cases there has been a tendency for the curve of the urine sugar concentration to follow that of the blood sugar. In others this has been directly the opposite. Closer inspection of the data shows that the real parallel is between the volume of the urine sample and the sugar concentration in it. With the small volumes often observed following the use of the 100 gm. of sugar in 200 cc syrup, the concentrations usually rose somewhat. Where there was diuresis, from drinking more water, the change was directly opposite. The concentration of the sugar in the urines of these different subjects was not uniformly decreased after the insulin. This inclines us to the point of view<sup>7</sup> that the sugars in the urine represent unusable sugars of the diet, and not the normal blood sugar escaping constantly, dependent on the blood sugar level. A slight glycosuria might well be found after such a tolerance test, using the juice of a lemon, and glucose of 99.4 per cent purity.

We feel that these results are of clinical importance in demonstrating that in the treatment of a diabetic the effect of a given dose of insulin can only be determined by the study of the blood sugar of that individual at intervals of not more than a few hours during a typical day. The choice of the particular times for taking blood samples with relation to meals and the dosage of insulin must be determined by experiment. The variable duration of the effects of insulin also make it important to know how long a given dose will show an effect in a certain diabetic, so that cumulative action may not be brought on with danger to the patient. Unless the patient is under careful control at all times, and the effect has been determined in his own case, it seems unwise to give two doses at less than six-hour intervals. The disadvantages of large doses given only once or twice daily in severe diabetics are apparent from the sudden reduction in blood sugar concentration which may follow in normals. We hope shortly to publish data from



the treatment and study of diabetics illustrating these points more in detail.

We have tried spraying insulin into the nostrils with an atomizer, but without effect. Ten units were given a rabbit on each of two days without any symptoms, and without a reduction of blood sugar. One of us took 10 units, another 20 units in a similar fashion, after fasting fourteen hours. There were no symptoms and no reduction of the blood sugar level.

**Conclusions.** 1. In normal human subjects the extent and the duration of the hypoglycemia after the injection of insulin are so variable that the result cannot be predicted from the dose per kilo of body weight.

2. The extent of the hypoglycemia and the duration of the low level are roughly parallel to the dose of insulin.

3. The depression of the sugar tolerance curves by insulin is not uniform in type or extent.

4. With increasing dosage of insulin both the extent and the duration of hypoglycemia are increased.

5. The blood sugar concentration at which symptoms of over-dosage of insulin appear vary in different individuals in the region from 40 mg. to 65 mg. per 100 cc of blood.

6. The concentration of sugar in the urines of normal subjects does not follow the blood sugar level with or without insulin. It is related more closely to the urine volume.

7. The treatment of diabetics with small doses of insulin at intervals of not less than six hours is preferred to the use of larger doses at very long intervals, or of smaller doses at too short intervals.

8. Intranasal application of insulin is without effect.

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# A REPORT OF SIXTY-FOUR CASES OF DIABETES MELLITUS TREATED WITH INSULIN.

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THE great addition to our therapeutics given us by Banting<sup>1</sup> and his colleagues, namely, the insulin treatment of diabetes, is still so new that reports from the clinics where it is being employed are of value. On the medical service of the hospital of the University of Pennsylvania there have been treated 64 cases, and it seems desirable at this time to present certain observations made in connection with the insulin treatment of these cases.

The classification of the cases by age and severity is presented in Table I. The first group includes cases with no diacetic acid in the urine on admission. The second group includes cases with reduced CO<sub>2</sub> content of the plasma and with diacetic acid in the urine but with normal plasma PH. The third group includes cases with a lowered plasma PH in addition.

TABLE I.—NUMBER OF CASES ARRANGED ACCORDING TO AGE AND SEVERITY.

Age, years.	0-10	10-20	20-30	30-40	40-50	50	Total.
Mild . . . . .	1	5	6	5	5	25	47
Lowered alkali reserve . . . .	0	0	1	2	1	2	6
Lowered Alkali reserve low PH .	0	2*	3*	4*	1*	1*	11
		+	+++	++++			
Total . . . . .	1	7	10	11	7	28	64

+ Associated acute infection.

\* Coma.

The diets for the cases reported in this paper were prepared in a special kitchen under the supervision of an experienced dietitian. In the control of the treatment the following analyses were used: The hydrogen-ion concentration by the colorimetric method of Cullen;<sup>2</sup> urine ketones by the method of Van Slyke;<sup>3</sup> blood ketones by the method of Van Slyke and Fitz;<sup>4</sup> blood-sugar concentration by the method of Folin and Wu;<sup>5</sup> plasma CO<sub>2</sub> content and CO<sub>2</sub> capacity by the method of Van Slyke.<sup>6</sup> Most of the plasma CO<sub>2</sub> observations given in this paper represent content, but in a few

instances, indicated by an asterisk, the capacity is given. Acetone was determined qualitatively by the sodium nitroprusside test and diacetic acid by the ferric chloride reaction.

**Treatment of Mild Cases.** These patients were placed on a diet of 100 gm. of fat, 50 gm. of carbohydrate and 1 gram of protein for each kilo of body weight. If there was a glucosuria on this diet one dose of insulin, usually 5 units, was given twenty minutes before the noon meal. If a further increase was necessary a dose, usually 5 to 10 units, was given twenty minutes before breakfast and the same amount before supper. If necessary, larger doses were given before breakfast and supper or 10 units were given before each meal. When the urine became sugar- and ketone-free carbohydrate and fat were increased to furnish a maintenance diet. As the diet was increased the dosage of insulin was increased, if necessary, to prevent glucosuria and acetonuria and to maintain a fasting blood-sugar level between 0.12 and 0.15 per cent. The amount of fat allowed was within the limit of a ketogenic-anti-ketogenic ratio of 1.5 or less.

The insulin dosage of our mild cases varied from 5 units once a day to 30 units a day. We have observed in some patients that have been placed on a relatively liberal diet that the dosage of insulin must be increased at intervals to take care of the same quantity of food, even though there has been no gain in weight.

**Treatment of Severe Cases.** Seventeen patients showed a reduction of the  $\text{CO}_2$  content of the blood below normal and the presence of a marked diacetic acid reaction in the urine, and 9 of these showed a reaction of the blood more acid than normal as determined by the  $\text{PH}$  of the plasma. Five of the 17 cases were admitted in coma. Eleven of the 17 cases were thrown into a critical condition by acute infections such as tonsillitis, pneumonia, upper respiratory infections or local pyogenic infections.

The treatment of these 17 patients varied with the degree of severity. If the patient showed a normal plasma  $\text{PH}$  the tolerance for carbohydrate was determined before insulin was given. If the patient showed a diacetic acid reaction in the urine and an acidosis as indicated by a lowering of the  $\text{CO}_2$  content of the plasma and a fall in the plasma  $\text{PH}$ , a diet was given low in fat containing an amount of protein equal to 1 gm. per kilo of body weight and sufficient carbohydrate to safely balance the insulin, usually from 100 to 150 gm. per day. Ten to 15 units of insulin were given three times a day twenty minutes before each meal with, in some instances, a fourth dose at midnight. When the reaction of the blood became normal and the diacetic-acid reaction disappeared from the urine the insulin dosage and the diet were gradually adjusted until the patient could take if possible 800 to 1000 calories above the basal requirement and remain aglucosuric and free of ketones. The basal requirement was determined by the height-

weight formula of Du Bois.<sup>7</sup> The amount of fat to be given was calculated by the Woodyatt<sup>8</sup> formula so that the ketogenic-anti-ketogenic ratio should be 1.5 or below. The shift of the acid-base equilibrium in the cases treated with insulin is discussed in a paper by Cullen and Jonas.<sup>9</sup>

**Case Reports.** From the 17 severe cases the following typical ones are described in detail:

CASE I.—Ins. No. 22: M. W., a male, white, aged thirty-five years, Hungarian, was admitted to the medical division of the hospital, March 12, 1923. The symptoms of diabetes had been discovered a year before. As in so many cases the carbohydrate tolerance had been slightly below normal at the beginning, but gradually had become less until a marked restriction of carbohydrate was necessary to keep him aglucosuric. He had lost 30 pounds in the last year, and at the time of admission was weak. On admission his weight was 100 pounds, his height five feet five inches. There was no edema. The  $\text{CO}_2$  content of the plasma was 38 volumes per cent; the  $\text{PH}$  of the plasma, 7.26; the blood-sugar concentration, 0.296 per cent. A twenty-four-hour collection of urine yielded 7.02 gm. of ketones in terms of acetone, 9.42 gm. of nitrogen and 112.5 gm. of glucose. The patient was placed on 50 gm. of protein, 20 gm. of fat and 100 gm. of carbohydrate per day and 10 units of insulin three times a day, twenty minutes before each meal. The third day after admission the  $\text{CO}_2$  content of the plasma was 73 volumes per cent.,  $\text{PH}$  7.4 and the urine gave a negative diacetic acid reaction. On the fifth day the  $\text{CO}_2$  content of the plasma rose to 81 volumes per cent and the  $\text{PH}$  to 7.46, the urine was alkaline and free of ketone. Bicarbonate of soda had not been given. The diet was then changed to 50 gm. of protein, 160 gm. of fat, 50 gm. of carbohydrate per day. The urine became sugar-free in a few days, and the fasting blood sugar fell to 0.142 per cent. The fat and carbohydrate were then gradually increased until the patient was taking 100 gm. of carbohydrate and 2400 calories per day. His basal requirement was calculated as 1410 calories. On the latter diet and 10 units of insulin before each meal, the urine remained sugar-free throughout the twenty-four hours, except occasionally during the night. He was discharged on April 21, 1923, in good condition. He weighed 114 pounds when discharged.

The other severe cases adequately treated with insulin responded equally well except that the gain in weight was not as marked as in the patient cited. This phase of the response to treatment will be discussed later. All of these patients on discharge were taking a maintenance diet with two or three doses of insulin, totaling not more than 30 units a day, were free from glucosuria, had a normal plasma  $\text{CO}_2$  content and  $\text{PH}$  and showed no diacetic acid in the urine.

**Cases of Coma.** Previous to the use of insulin, patients in diabetic coma, with few exceptions, died. Cases of coma treated with insulin are now often rescued from death. When insulin becomes more generally used diabetic coma should become less frequent. In the treatment of coma the results from insulin are most spectacular.

Five cases of diabetic coma are included in this series. However, 2 patients died within an hour after admission. Therefore, only 3 of the cases were adequately treated with insulin and all of these recovered. Because of the unusual features the histories of 2 of these cases of coma are given in detail.

**CASE II.**—Ins. No. 5: M. I., white, female, American, aged thirty-four years, was admitted to the hospital, November 16, 1922. Two years before admission she began to have polydipsia and polyuria and gradually lost weight. On admission she weighed 91 pounds. She was untreated until November 12, 1922, when a physician was called to treat an acute gastro-intestinal attack. A diagnosis of diabetes was made and the patient immediately put on a restricted diet. On November 14, respiratory distress developed. On the evening of November 15 she became delirious and then stuporous. She was admitted to the hospital in the afternoon of November 16.

On admission she was in coma, from which she could not be aroused. There was marked respiratory distress. She was given intravenously 500 cc of a solution containing 5 per cent of glucose and 2.5 per cent of bicarbonate of soda. One hour later blood was taken from a vein at the elbow for analysis. The  $\text{CO}_2$  capacity was 17 volumes per cent; the blood-sugar concentration, 0.411 per cent. The urine showed a marked glucosuria and ketonuria. After the venous puncture 20 units of insulin were given hypodermically. Within two hours she could be aroused. Ten units were given five hours later. Protocol No. 1 gives the progress of the case during the first fourteen days of her stay in the hospital.

The analysis of the protocol shows that relatively small doses of insulin may rescue a patient from coma. The shift of the acid-base equilibrium was most striking. In four days it passed to the alkaline side of normal. The urine was alkaline at the height of the shift. On the eighth day the plasma reaction again changed to the acid side of normal following a reduction in the dosage of insulin, because of an inadequate supply. After the dosage of insulin was increased the reaction passed in forty-eight hours to the alkaline side. The quantity of ketones in the blood fluctuated with the acid-base equilibrium.

On the morning of the tenth day the patient again became somewhat stuporous. There was no evidence, however, of Kussmaul breathing and analysis of the blood and urine showed a picture

## PROTOCOL NO. 1.—CASE.—INS. NO. 5.

Day ending.	Diet per day.				24-hr. urine.				Plasma.		Blood.		Insulin units per day.
	Protein, gm.	Fat, gm.	Carbo-hydrates, gm.	Calories.	Glucose, gm.	Acetone.	Diacetic acid.	Total N, gm.	CO <sub>2</sub> volume, per cent.	pH.	Ketones, gm. per liter.	Glucose, per cent.	
11-16	..	..	..	....	xx	xxx	xxx	....	*17	....	....	.411	32
17	..	..	..	....	6.8	xxx	xx	....	...	....	1.27	.265	32
18	..	..	..	....	....	....	....	....	†41	7.34	....	.313	32
19	..	..	..	....	20.0	xx	x	....	...	....	....	....	32
20	..	..	..	....	2.9	xxx	x	....	†66	7.50	.18	.200	24
21	41	31	32	476	26.4	8.42 gm.	...	5.92	...	....	....	....	16
22	45	31	29	559	40.2	xxx	xx	....	...	....	....	....	16
23	45	27	25	526	3.9	xxx	xxx	....	†29	7.24	.84	.174	32
24	43	34	34	460	tr.	x	0	....	†60	....	....	....	32
25	40	33	29	569	....	....	...	....	†73	7.48	....	0.35	32
26	41	27	60	672	5.7	0	0	....	...	....	....	....	32
27	46	28	81	797	4.9	x	0	4.20	...	....	....	....	32
28	48	29	88	832	tr.	x	0	....	...	....	....	.094	32
29	53	73	85	1239	....	....	...	....	†71	7.54	....	....	32

\* = capacity. † = content. xxx = strong reaction. xx = moderate reaction. x = weak reaction.

quite different from that of coma. Urine obtained by catheterization showed no sugar or ketone. The blood-sugar concentration was 0.035 per cent. About 25 gm. of glucose were given at once, and she recovered in a few minutes from the stupor. When discharged, December 22, 1922, she was receiving 8 units of insulin before each meal with 80 gm. of carbohydrate per day and remaining aglucosuric and free of ketone. At the present time, seven months after discharge, on 10 units of insulin twice a day, before breakfast and supper, she is able to carry on her household duties.

CASE III.—Ins. No. 11: T. C., male, white, American, aged eighteen years, was admitted to the ward, February 11, 1923. The onset of diabetes was in February, 1921, after an attack of mumps. With the exception of a few weeks of hospital treatment in July, 1921, he had been untreated. On February 6, 1923, he developed acute tonsillitis, which rapidly brought about the present crisis. On admission, it was difficult to arouse him. He presented a classic picture of severe diabetes. Air-hunger was marked. Examination of the urine showed sugar and much diacetic acid. Protocol No. 2 presents his progress during the first six days in the hospital.

The outstanding features of his case are the plasma PH 6.98, which up to this time is the lowest, we believe, recorded with recovery, and the rapid shift of the acid-base equilibrium from markedly increased acidity to the alkaline side of normal. At the outset 10 units of insulin were given every six hours. After two days the dosage was reduced to 30 units per day.

On March 19, because of a break in diet, acidosis developed. The PH of the plasma passed to 7.22 and the CO<sub>2</sub> content to 38 volumes per cent. Ten units of insulin, every sixth hour for three days, restored his acid-base equilibrium to normal. He was discharged from the hospital, May 21, 1923, sugar-free and ketone-free, on 10 units of insulin three times a day with 80 gm. of carbohydrate per day and a total caloric intake per day of 1700 calories.

It is of interest to compare these relatively small doses of insulin with the massive doses used in some other clinics in the treatment of coma. It is possible, of course, that the dosage described above would not prove adequate for the treatment of all cases of coma.

Bicarbonate of soda was not given to these cases because we desired to follow the shift of the acid-base equilibrium in severe acidosis treated with insulin and without alkali therapy. As a routine, we had been accustomed to give bicarbonate of soda to cases of diabetic coma. Cases of acidosis not in coma have not been given alkali because when insulin is used the acid-base equilibrium rapidly becomes normal.

**Diabetes with Intercurrent Infections.** Intercurrent infections either mild or severe usually cause a reduction of the carbohydrate

## PROTOCOL NO. 2.—CASE.—INS. NO. 11.

Day ending.	Diet per day.				24-hr. urine.			Plasma.			Blood.		Insulin units per day.
	Protein, gm.	Fat, gm.	Carbo-hydrates, gm.	Calories.	Glucose, gm.	Acetone.	Diacetic acid.	Total N, gm.	CO <sub>2</sub> volume, per cent.	pH.	Ketones, gm. per liter.	Glucose, per cent.	
2-12	28	8	269	1266	120	xxx	xxx	18.5	*16	*6.98	*.370	*.326	30 } 10 units
13	27	14	122	733	29	xx	0	...	44	7.32	.110	.306	40 } every 6
14	35	18	147	904	84	xx	0	10.4	64	7.51	.074	.153	40 } hours.
15	42	16	99	720	36	xx	0	...	58	7.42	.....	.....	30 } 10 units
16	39	20	39	498	8	x	0	8.12	58	7.43	.....	.190	30 } before
17	47	20	79	702	tr.	x	0	...	.....	.....	.....	.....	30 } each meal.

\* = before insulin.    xxx = strong reaction.    xx = moderate reaction.    x = trace.



tolerance, and in many instances have led to coma and death. Surgery on diabetic patients has been especially dangerous because of the high mortality among operated patients. Six of our cases exhibited intercurrent infection, 4 of the 6 being cases of diabetic gangrene, 1 a patient with carbuncles and another with lobar pneumonia. Insulin diminishes the seriousness in these cases. Its efficacy in the control of diabetes during acute infections was striking in all 6.

**The Effects of Insulin on Blood-sugar Concentration.** Early in our experience with insulin we observed a mild insulin reaction, weakness and sweating in the afternoon, in spite of the presence of glucose in the twenty-four-hour collection of urine and a hyperglycemia in the morning before injecting insulin.

The following studies were, accordingly, made. Blood-sugar concentration was determined, beginning before the first dose of insulin for the day and continuing at intervals until 9 or 10 o'clock at night. Specimens of blood were taken every hour, or hour and a half, and immediately before each insulin dose and just before taking food. A specimen of urine was collected, when possible, immediately after each venous puncture and examined for sugar, acetone and diacetic acid.

The results of four such experiments are plotted in the charts. The amount of carbohydrate and the dosage of insulin together with the time of administration are represented by columns, solid for insulin, hatched for carbohydrate; the scale of plotting for the insulin and carbohydrate is so chosen that columns of equal height indicate insulin and carbohydrate in the ratio of 1 unit of insulin for 2 gm. of carbohydrate. This is the ratio which Campbell and Fletcher<sup>10</sup> give as a balancing ratio in suitable cases. The patient whose curve is represented in Chart I received no carbohydrate for breakfast, 36 gm. at noon, 23 gm. at supper and 5 units of insulin before breakfast and supper and 10 units at noon.

The patient whose curve is shown in Chart II received no carbohydrate for breakfast, 46 gm. at noon and 23 gm. at supper, and 5 units of insulin before breakfast and supper and 10 units at noon.

The patient whose curve is shown in Chart III received no carbohydrate for breakfast, 41 gm. at noon and 33 gm. at supper and 10 units of insulin before each meal. This patient, on this regimen, had been aglucosuric and free of ketone two days before this experiment. The cause of the sudden ketonuria and glucosuria is probably that the patient, who was somewhat unreliable, had taken unauthorized food the day before the experiment. Two days later on the same regime diacetic acid was not present in the urine and only a trace of sugar.

The patient whose curve is shown in Chart IV received 80 gm. of carbohydrate per day and 10 units insulin before each meal. Her twenty-four-hour collection of urine had a trace of sugar.

Her curve illustrates well the morning hyperglycemia. Food was last taken at 6 P.M. At 8.30 P.M. there was a slight insulin reaction with hypoglycemia. The next morning there was marked hyperglycemia.

The patients whose curves are plotted in Charts I and II, respectively, received 5 units of insulin before breakfast and supper and 10 units at noon. The largest dose of insulin was given at noon because that meal contained the largest portion of carbohydrate.

The hypoglycemia shown in Chart I accounts for the mild insulin reaction observed in this patient in the afternoon.

Inspection of the charts shows a drop in the blood-sugar concentration during the day and a rise during the night. The minimum value occurred in the afternoon or early evening and coincided with the time at which hypoglycemic reactions, characterized by weakness, sweating and headaches, had been noted in patients receiving similar insulin treatment.

In explanation of the time relations shown in these curves it is possible that we are dealing during the afternoon with an accumulation of insulin from both morning and midday doses. It is possible also that there is a delay in the response of the blood-sugar curve to the ordinary complex-carbohydrates of the diet, due to the time consumed in digestion and absorption. It would seem that such delayed response to carbohydrate ingestion is the important factor in the first three charts. Approximately one hundred and eighty minutes elapsed before the carbohydrate of the food influenced the blood-sugar concentration in these cases. This contrasts sharply with the prompt effect of administering pure glucose by mouth, as was done in Case Ins. No. 5 for the relief of the symptoms of hypoglycemia. In Chart IV both the accumulating effect of the insulin and the delayed response to the carbohydrate of the meals are apparent.

These observations suggest that the amount of insulin sufficient to balance the carbohydrate of the meal, might to advantage be given at a time interval after the meal rather than before it. It is possible that such a regimen would lead to a more even blood-sugar regulation and avoid the symptoms of hypoglycemia as well as the night hyperglycemia and glucosuria.

The promptness with which symptoms of insulin hypoglycemia develop when the balancing carbohydrate is not provided, is strikingly illustrated by one of our cases. A child, aged three years, had been admitted because of diabetes. Her urine was ketone-free. She was in a fair state of nutrition. On 5 units of insulin, before each meal, and 35 gm. of carbohydrates per day her twenty-four-hour collection of urine was seldom entirely free of glucose. This diet consisted of eggs, chicken, butter and 5 per cent and 10 per cent vegetables. On a certain day, although her condition had seemed satisfactory, an hour after supper she suddenly

had convulsions, which were tonic and clonic and lasted eight minutes. Shortly after the convulsions she vomited. The vomitus contained most of the food taken at the noon meal and nearly all of her evening meal. Following the vomiting she became stuporous. The blood-sugar concentration at this time was 0.03 per

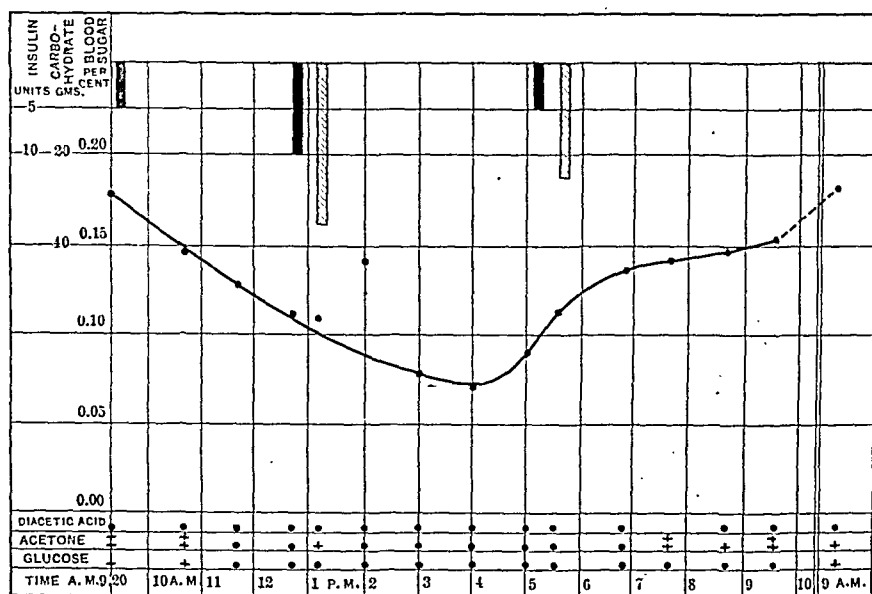


CHART I.

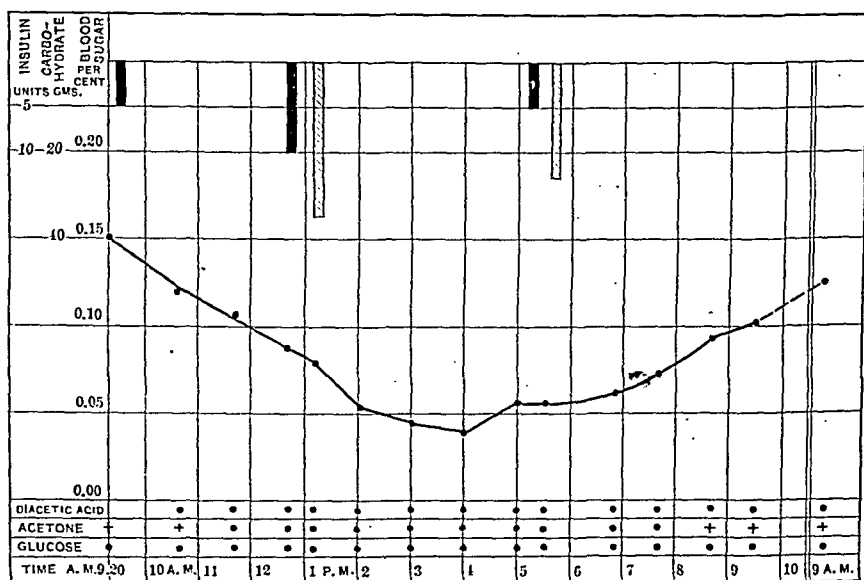


CHART II.

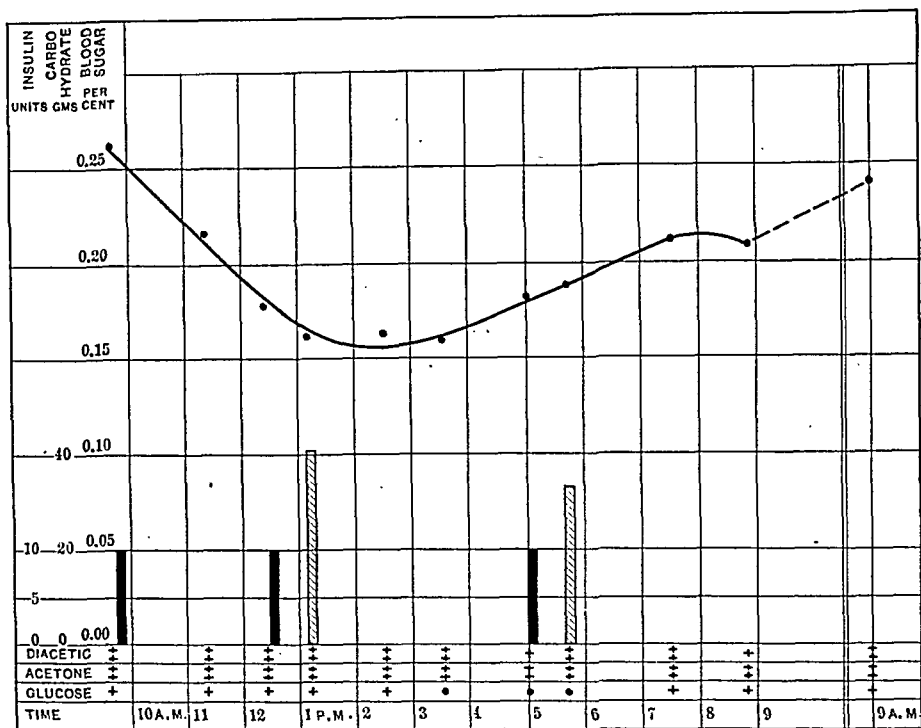


CHART III.

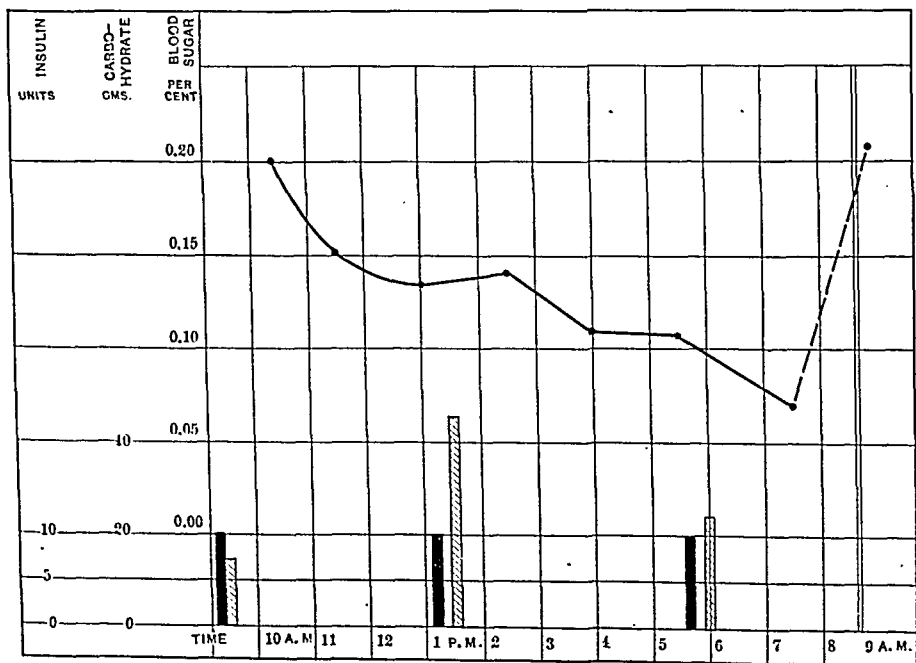


CHART IV.

Curve: blood-sugar concentration; Solid columns: insulin dosage; Hatched columns: carbohydrate in food.

Diacetic acid, acetone and glucose: qualitative reaction in twenty-four-hour urine: • = none; + = slight; ‡ = marked.

cent. Thirty gm. of glucose in a 5 per cent solution were given intravenously and the child slowly recovered. In two hours she had returned to her usual state of health. We concluded that, due to failure of digestion, the balancing effect of the carbohydrates of the diet on the insulin had not occurred.

Another example of hypoglycemic stupor has been given in the description of Case Ins. No. 5.

**Weight.** One of the effects of insulin particularly in the undernourished has been gain in weight and strength, a result not attainable in most cases by previous methods.

In our study of insulin therapy we have observed that the gain in weight has been a slower process than we had expected. Of our patients, 34 out of 64 did not gain weight; 27 out of 64 patients were at discharge 2 pounds or more heavier than their lowest weight in the hospital; 2 gained 20 pounds, 4 gained between 10 and 15 pounds; 9 gained between 5 and 10 pounds; and 12 gained between 2 and 5 pounds. Of the 2 who gained 20 pounds, 1 (Case Ins. No. 11) remained in the hospital three months and ten days, while the other (Ins. 4) remained eight and a half months. In both instances the gains in weight were slow and did not begin until the patients had been in the hospital for a number of weeks. Those gaining from 10 to 15 pounds were in the hospital from five weeks to two months. The minimum stay for those gaining 5 to 10 pounds was three weeks. Those who were in the hospital less than two weeks as a rule did not gain. In many cases the patients did not gain weight on a diet of a 1000 to 1200 calories above their basal requirements. Since the basal requirement was calculated for a normal individual of the same age, sex and surface area, and since the plane of metabolism is lowered by loss of weight and dietary restriction one can assume that the allowance was liberal for a diabetic. Our conclusion is that gain of weight is not immediate even on very liberal diets. Apparently an adjustment must take place before a gain in weight begins.

**Summary.** 1. The effect of insulin treatment in 64 diabetics is discussed.

2. Three cases of diabetic coma with recovery under insulin are reported and 2 described in detail.

3. The value of insulin treatment during intercurrent infection in diabetes is noted.

4. The blood-sugar concentration was measured at frequent intervals throughout a day in 4 patients on insulin treatment and the resulting curves constructed. The time relations apparent in the effect of insulin and of the carbohydrate feedings are charted and certain implications as to the timing of the insulin dosage are discussed.

5. A delayed gain of weight on insulin therapy is noted.

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## THE TREATMENT OF DIABETIC COMA WITH INSULIN.\*

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UNTIL the last year it has not been my good fortune to see a recovery from diabetic coma. There are reports in the literature it is true, that recovery has taken place, but with possibly one or two exceptions, coma quite promptly recurred and led to death. Since October, 1922, 15 cases of diabetic coma have been treated; of these 8 recovered from the coma and of these 8 who recovered, 5 are still alive. These cases were treated within insulin. Having a means of controlling the primary acidosis factor in coma, we have been able also to study secondary, contributory factors and devise means to combat them. There seems to be three abnormal conditions which are notable in all cases of diabetic coma; acidosis, desiccation of the tissues, and myocardial weakness. While acidosis is primary and in a sense probably initiates other disorders in the body-chemistry, it is also true that death may result from one or both of the secondary factors after the acidosis has been corrected. Some years ago when the causation of diabetic coma was still uncertain, Magnus-Levy asserted that the theory of

\* Read as part of a symposium on insulin treatment at the meeting of the Association of American Physicians,

death from acidosis must be accepted unless treatment with alkalis had been successful to the degree of rendering the urine alkaline. We no longer measure degrees of acidosis by urine examinations, but death may occur in diabetic coma after the blood no longer gives evidence of acidosis and there are now several reports of death in diabetic coma after the urine had become alkaline. I have seen one such case. Therefore I wish to emphasize that other factors than acidosis demand attention in the treatment of diabetic coma and that they cannot be neglected.

Everyone who has seen cases of diabetic coma must have been impressed by the evidence of desiccation of the tissues. Although there may be no fever, the mouth and pharynx are invariably dry and parched to a degree usually seen only in febrile disease. The reduced intraocular tension is also probably an effect from water loss. As a matter of fact, every case of severe diabetes presents evidence of the difficulty of maintaining the water balance in the body. Now, as acidosis becomes more and more severe two conditions develop which prevent the patient from drinking adequate amounts of fluid. He is often nauseated; sometimes he vomits and although the thirst be agonizing he fears to drink, or vomits when he does drink. In the course of hours he becomes drowsy and drinks less and less as stupor creeps on him. In brief, less water is taken into the body as acidosis progresses. But during this period the water elimination does not decrease. The glucose excretion is extreme and persistent and constantly abstracts water from the tissues for urine formation. Pulmonary ventilation is increased and augments the water loss of the expired air. Even the small amount of endogenous water is diminished, since both carbohydrate and fat, which normally are burned to carbon dioxide and water, now are not oxidized (glucose), or are oxidized only to intermediate ketone bodies. A moment's thought on these abnormal conditions clarifies the extreme desiccation which is notable in cases of diabetic coma. The significance of desiccation alone as a cause for abnormal metabolic states was demonstrated in the classical experiments of Woodyatt.

It has been recognized for years that when fluids are injected intravenously in cases of diabetic coma an especial care must be exercised or death may suddenly occur. The fluid must be given more slowly than is necessary in other diseases, and the amount injected at one time must be small. It is a general belief, I think, that the myocardium in diabetic acidosis is seriously damaged and must be protected. The hearts of young subjects examined at autopsy, show hypertrophy and cloudy swelling of the muscle. During life there is usually tachycardia, and occasionally delirium cordis. On one occasion it happened that a patient came out of coma and conversed about his disease and then developed symptoms which seemed typical of acute cardiac failure and died. There

is nothing definite and little is known of the vascular mechanism in severe acidosis. But until we possess a better understanding it seems wise to use the general measures employed when a similar train of signs is presented.

There is no means of determining in an individual case the amount of insulin which will be required to stop the formation of ketone bodies. The smallest amount effective in my series was 70 units given in a period of six hours, and the largest dosage used in a case that recovered was 180 units during twelve hours. In the beginning our dosage was too small because we had to economize in insulin. Now we are more liberal. In such a critical condition the best rule is to be sure that one uses enough. The first dose may be 25 units at least, in adults, and repeated smaller doses at intervals of an hour or two. The urine should be tested for sugar every two or three hours and heavy dosage is advisable, so long as large amounts of sugar are excreted. When the sugar in the urine begins to fall, then the dosage of insulin can be decreased and the interval between doses lengthened. It is evident from numerous observations, both in coma and severe acidosis, that the blood sugar is most variable and apparently has no clear relation to the clinical symptoms. The concentration may be as low as 250 mg. per cent, a not uncommon figure in many cases in good condition and free from ketonuria. Then, too, it has been observed that the blood sugar may be higher after the patient has recovered from coma than it was during coma. This is probably due to the glucose given in the rectal instillations.

That adequate amounts of glucose be available in the tissues seems to me important. Acidosis is initiated by failure of the oxidation of glucose. Progressively, then, fat and protein are substituted as sources of energy. The glucose from protein not being utilized, the metabolism of fat is progressively imperfect. The primary object in treatment is to substitute a carbohydrate metabolism for a dominant fat metabolism. Insulin makes it possible to accomplish this end but only when glucose is available for oxidation after insulin is given. Therefore, it is logical, in our opinion, to use glucose in clysters and in beverages. For the latter, orange juice is satisfactory and gratefully taken.\*

The use of alkalis in severe acidosis has been a debated subject. On purely theoretical grounds, there is ample basis for the administration of large doses of bicarbonate of soda. Underhill's experiments some years ago suggested that more sugar was utilized when alkalis were administered and Mosenthal has recently applied this principle to human subjects. During coma little liquid can be given by mouth and the amount of alkaline salts which can be

\* For rectal instillations Karo syrup is an available source of glucose. Two ounces to the pint of water makes a solution of approximately five per cent strength. Only pure dextrose may be used intravenously.



given intravenously is insignificant. We have used 3 per cent bicarbonate of soda solution along with glucose for rectal instillations and by the Murphy drip method. Any good effect of the alkali, *per se*, is obscured because of several measures employed simultaneously. Physiological saline solution has been used for hypodermic and intraperitoneal injections and 3 per cent sodium bicarbonate solution intravenously.

The variation in procedures in different cases is shown in the summaries of clinical records. The direct aims in our methods have been to arrest ketone formation by restoring an adequate oxidation of glucose; to relieve desiccation by introducing water into the body through every avenue of absorption; and finally to support, or stimulate the circulation by digitalis and caffeine.

CASE I.—Y. F., aged forty-eight years; was admitted to the private patients' building, October 4, 1922. She had had diabetes five years and a week before developed infection of her ring finger following the prick of a pin. Operation was performed October 4, 1922 (Dr. Hitzrot) and her left ring finger amputated with removal of the metacarpal bone; the flexor tendons were gangrenous and the wound was left open. Culture showed *Staphylococcus aureus*. October 7, the urine contained 2.7 per cent of sugar and was strongly positive for acetone. The blood sugar was 0.364 per cent. The patient was in profound coma. Murphy drip was started and 30 cc of iletin given during next six hours. She died at 6 P.M. This patient was a mild diabetic, her disease was temporarily severe and acidosis was initiated by infection. Had we had sufficient iletin we believe her life could have been saved.

CASE II.—G. H., aged sixteen years, had been a patient in the Methodist Episcopal Hospital in Brooklyn for a month before transfer to the New York Hospital. He was admitted in coma, October 3, 1922. Prior to transfer he had received 30 units of iletin. The typical signs of diabetic acidosis were present. The blood  $\text{CO}_2$  was 9.9 volume per cent, and the sugar 260 mg. During the first twelve hours this patient received 100 units of iletin and another 100 units during the following eighteen hours. Fluids were given by rectum at first, and as soon as the patient roused sufficiently by mouth also. The patient became conscious and rational about fourteen hours after treatment commenced. His food at first was 1 liter of milk per day with orange juice, later a measured diet. Recovery was perfect and he was discharged in November. He was faithful in executing directions and gained 10 pounds in weight on continued iletin treatment of 15 to 20 units per day. In February he contracted influenza and died, whether in coma, or not we do not know.

CASE III.—A. D., a woman, aged forty-seven years, who had had diabetes for an indefinite period. On account of diabetic gangrene, her left leg had been amputated just below the knee. Sugar had been eliminated from the urine before operation. The operation was followed by a fibrile reaction and sugar reappeared in the urine. December 26, 1922, two days after the operation, the patient was stuporous and had a temperature of  $101^{\circ}$  F.; her blood sugar was 0.3 per cent; urinary sugar approximately 2 per cent, and acetone was present. By the use of 50 units of iletin in the next twenty-four hours urinary sugar was reduced to a trace and the blood sugar reduced to 0.17 per cent. The blood  $\text{CO}_2$  was raised from 20 to 40 per cent. On the appearance of gas bacillus infection in the wound, iletin treatment was abandoned.

CASE IV.—J. C., aged twenty-one years, gave a six-day history of extreme polydypsia and polyuria. Thirty-six hours previous to admission he felt very weak and faint. Twelve hours previous to admission he seemed to be somewhat delirious and six hours later became comatose and remained so until he was brought to the hospital. Examination of the urine by his doctor had shown sugar of 4 per cent but no acetone or diacetic acid. No albumin or casts were present. The patient was told he had diabetes and was referred to the hospital. Past history revealed that he had gained weight from 140 pounds to 230 pounds, his present weight, in the course of the last three years. His father and mother were both rather obese but not particularly large.

Physical examination showed a very obese young man with flushed skin in deep coma. His respirations were 55 per minute and the pulse rate 120. There was suggestive acetone odor on his breath. The heart sounds were very distant and the second sound was scarcely audible. His blood-pressure was 86/56. Examination of the eye grounds disclosed nothing abnormal. A diagnosis of diabetic coma was made and the patient was treated with iletin injections and Murphy drip of 2 per cent glucose and 2 per cent sodium bicarbonate. As the heart was evidently failing he was given 4 ampules of digifolin subcutaneously. The patient did not recover consciousness but died after eight hours, having developed edema of the lungs. Immediately after death the bladder was catheterized but only 25 cc of urine was obtained. *This showed sugar and a faint trace of acetone.* Nothing abnormal was found in the postmortem examination. Blood taken four hours after death had a sugar content of 1.058 per cent. Non-hemolytic streptococci were grown from the blood culture.

CASE V.—Mrs. N. S., aged twenty-eight years, developed diabetic coma December 9. She had had diabetes about a year and had failed in health rapidly. Her treatment in the past seemed to

have been rather indefinite. On December 8 and 9, she had felt sick and the bowels had not moved for several days. The patient was emaciated, weighing 85 pounds. The face was flushed and the respirations were characteristic of acidosis. She was not in deep coma but could be roused, not, however, sufficiently to answer questions. The blood sugar was 450 mg. per cent and the  $\text{CO}_2$  13 volume per cent. The routine method of treatment was used and 5 units of iletin were given every two hours. As soon as the patient was sufficiently conscious, a matter of six hours, she received milk and orange juice. On December 13, the total glucose tolerance was determined to be 60 gm. (including glucose, from protein, determined on the basis of urinary nitrogen). A diet containing 1000 calories was ordered and with 10 units of iletin daily the patient maintained a sugar-free urine and was sent home December 22, weighing 89 pounds.

CASE VI.—S. B., aged thirty-six years, was transferred from Bellevue Hospital to New York Hospital January 1, 1923. The patient was unable to speak any language familiar to the staff and the only history was of severe diabetes recognized at Bellevue. He was admitted in deep coma although he had had 50 units of iletin during the six hours before his transfer. The usual routine treatment was carried out and 5 units of iletin were given every two hours. The patient recovered from coma in about ten hours. As soon as consciousness returned the patient commenced to vomit and this continued at short intervals. Examination revealed signs suggesting acute dilatation of the stomach. This was treated by gastric lavage and no fluids were given by mouth. In spite of this obstacle the patient continued to improve and the urine was free of sugar on the fourth day. He left the hospital against advice, but has only recently returned to Bellevue for treatment (April).

CASE VII.—D. G., aged fifty-one years, had had diabetes of a mild type for a number of years. In the latter part of December he took cold which resulted in bronchitis and then pneumonia. He became stuporous during the day of January 2 and was in coma when seen January 3. Samples of blood were not secured at the first examination. He was given 5 units of iletin every three hours. Consciousness returned in ten hours and the blood sugar was then 0.306 per cent and the  $\text{CO}_2$  32 volume per cent. The iletin dosage was decreased and everything progressed favorably for a week. We then ran out of iletin and this patient had none for five days. His diet at the time iletin was discontinued contained 1400 calories. It was reduced to 770 calories (P. 40, C. 40, F. 50). The blood sugar was then 0.174 per cent. On the sixth day coma developed a second time and having received a new stock of iletin 25 units

were given in one dose and 10 units every two hours. Consciousness returned completely after about twelve hours.

The patient died January 23, of pulmonary abscess.

CASE VIII.—M. L., aged six years, was admitted February 6, 1923, with a history of diabetes of three years' duration. The child became drowsy about twenty-four hours before admission to the hospital. The temperature was 99.8° F., pulse 135, respirations 40. The patient was drowsy and the tongue and pharynx were dry. The reflexes were present but sluggish. She was able to swallow and orange juice and water were given. Glucose in a 5 per cent solution was administered by Murphy drip and 200 cc was absorbed in the first six hours. The first dose of iletin was 25 units and three hours later 10 units; 70 units were given in all in the first fifteen hours. The urine then contained no sugar and the blood sugar was found to be 0.047 per cent. There were no signs of shock but iletin was discontinued temporarily. For the first two days milk alone was given and then a standard diet. This patient is receiving 12 units of iletin per day which enables her to utilize a diet of 1100 calories. She has gained in weight and her condition is satisfactory.

CASE IX.—H. W., male, aged twenty-eight years, was admitted to private pavillion, February 6, 1923. He was said to have had diabetes two years. For four days he had complained of headache, anorexia, nausea, and constipation. On the morning of February 6, he was given a colonic irrigation at 11 A.M. and became stuporous an hour later. At 6 P.M. the temperature was 101° F., pulse 112, and respirations 32. The patient was deeply comatose with typical respiration, soft eyeballs, immobile pupils and absent reflexes. Treatment consisted of soda bicarbonate solution intravenously and 5 per cent glucose by the Murphy drip method, black coffee by gavage and iletin. During three hours from 6.30 to 9 P.M., 90 units of iletin were given. Death occurred at 9.15 P.M. The blood taken just after death contained 0.375 per cent sugar.

CASE X.—Patient M. Z., aged thirty-three years, was admitted to the Second Division, New York Hospital, February 8, 1923, in the morning, in diabetic coma. The urine showed sugar, blood chemistry was not done. She was given an initial dose of 25 units of iletin and following that was given 10 units every three hours. A rectal instillation of sodium bicarbonate and glucose was given every four hours. The patient did not come out of coma and died the night of admission. She had been ill for only six months and there was a rapid increase of symptoms during the last week before admission. During the ten hours in the hospital she received 45 units of iletin. She had been in coma about six hours before admis-

sion and the duration of the coma was about fifteen hours. This patient received only 45 units of iletin, probably an inadequate amount.

CASE XI.—Patient L. T., aged twenty-six years, had been treated under Banting in Toronto in October, 1922. Iletin had been abandoned in January, and the patient had eaten freely. He was admitted to Lincoln Hospital in coma February 26, 1923, at 9.30 P.M., and was treated by my assistant, H. J. Spencer. The temperature was normal, pulse 150 +. The patient was emaciated and breathing in a typical way; the pupils were small and sluggish and the reflexes absent. Treatment consisted in the routine measures to relieve desiccation, and iletin. Seventy units were given in the first six hours and the patient became conscious and rational. The blood sugar was 0.395 per cent on admission and rose to 0.638 per cent at the end of twenty-four hours. Improvement was continued and the urine was free of ketones on the third day after admission. On a diet of P. 45, C. 52, F. 65, with 20 units of iletin per day; the sugar disappeared from the urine. Indefinite pulmonary signs led to roentgen-ray examination which suggested a resolving pneumonia. This patient is alive and doing well.

CASE XII.—Mrs. E. S., aged fifty-six years, developed diabetic coma February 28, 1923. She had had diabetes some seven years. The disease had caused little inconvenience until about six months ago. Since then there has been a rapid loss in weight and she has become too weak to leave her bed. The diet has been of the usual indefinite type and the urine, according to reports from commercial laboratories, had contained 3 to 6 per cent of sugar, also ketone bodies.

The patient was a small, very emaciated woman. Her face was sallow, slightly flushed and the respirations were rapid and deep. She was semi-comatose. The temperature was 96° F., pulse 100, respirations 30. The pupils reacted slightly, but other reflexes could not be elicited. The intraocular tension felt decreased. The blood sugar was 535 mg. per cent and the CO<sub>2</sub> 11 volume per cent. Treatment consisted of an enema followed by a 10 per cent glucose and 4 per cent soda bicarbonate instillation by means of the Murphy drip method. Twenty-five units of iletin were given at once and 10 units every two hours till the urine was free of sugar. This occurred at 8 P.M., March 1. The patient became conscious about fourteen hours after treatment was commenced. March 2, the blood sugar was 136 mg. per cent. From March 1 to 7 the diet consisted of 1 liter of milk and the juice of twelve oranges per day, 60 to 80 units of iletin were given daily in doses of 10 units each. March 7, the diet prescribed was P. 100, C. 150, F. 210; and this was changed March 13 to P. 70, C. 160, F. 100. She

was now receiving 40 units of iletin per day and sugar disappeared finally from the urine March 17. The patient was sent home March 20, having gained 10 pounds. The blood sugar ranged from 135 to 145 mg. per cent and the urine was free of sugar and ketones. Her present diet is P. 70, C. 100, F. 160; and 40 units of iletin per day is taken in two doses. Her condition is satisfactory.

The next case was the most difficult of any of those that survived. The acidosis factor appeared to be less pronounced than in some of the other cases but vomiting and impending cardiac failure were menacing features and only the tireless vigilance and courageous measures used by Dr. Hauser and Dr. Thompson of our staff saved the patient.

CASE XIII.—M. B., aged twenty-six years, was admitted to the hospital March 26, 1923. He had had diabetes about two years and had lost about 40 pounds. On the day before admission the patient had cramps in the abdomen, headache, and was short of breath. He was excessively thirsty but vomited whatever he drank.

At the time of admission the patient was drowsy. The temperature was 98° F., pulse 134, and respirations 42. Hypotension of the eyeball was noted and the reflexes seemed abolished. The appearance of the mouth and pharynx and the feeling of the muscles indicated severe desiccation. Iletin was given at once. The bowel was cleaned and instillations of glucose and soda started. After several attempts to give fluid by mouth, which induced vomiting, the stomach was lavaged and fluid by mouth discontinued. During the first twenty-four hours 900 cc of physiological saline was administered by hypodermoclysis. Small amounts of the saline were given intravenously and were injected into the peritoneal cavity. The pulse was small and rapid and at times cardiac failure was impending. For this caffeine and digitalis were given hypodermically. After the patient has been under treatment about twenty hours there was a sudden collapse. It seemed at the moment that this might be due either to heart failure or to excessive iletin. Glucose was injected into a vein and cardiac stimulants used. The condition gradually improved but not promptly. The iletin dosage had been liberal; 30 units were given on admission at 6 A.M.; 20 units at 7 A.M.; 15 units at 8, 9 and 10 A.M.; and 10 units every two hours thereafter till midnight when the urine was free of glucose.

The blood taken shortly after the first dose of iletin contained 357 mg. per cent of sugar and the CO<sub>2</sub> was 15.7 volume per cent. Four hours later the sugar was 250 mg. per cent and the CO<sub>2</sub> 24 volume per cent. After twenty hours the patient gradually improved and is now in excellent condition and taking a liberal diet.

CASE XIV.—D. G., aged thirty-one years, had discovered as a result of examination for insurance a year-ago that he was diabetic. He had had no symptoms till about three months ago. Two days before I saw the patient he had taken cold and had fever; the following day he was drowsy and feverish, and during the night had some difficulty in breathing. In the morning of February 5 he was semi-conscious. When I saw the patient with Dr. Schultheis at noon he was stuporous but could be roused to answer questions. Air-hunger was notable and the intraocular tension was reduced. The urine contained about 6 per cent of sugar and gave strong reactions for ketones. Blood taken at this time contained 0.656 mg. per cent sugar and the  $\text{CO}_2$  combining power was 14 volume per cent. The first dose of iletin, 20 units, was given about one o'clock and 10 units more at three o'clock. The usual supplementary measures were commenced. At three o'clock there seemed definite improvement; the patient was roused and discussed his treatment. About four o'clock the pulse became very rapid, 140, and later irregular and the patient seemed in collapse. Cardiac stimulants including adrenalin were given without notable result. During the next couple of hours the condition appeared more and more like that of cardiac failure. Dyspnea persisted but the respirations had lost the typical air-hunger character. Death occurred about six o'clock the same day.

The following case presented an unusual clinical picture. The signs in some respects were not those of diabetic coma, but the progress of the disease is most suggestive. It is unfortunate that adequate laboratory data are not available, the critical day of sickness having fallen on a Sunday.

CASE XV.—J. F., aged fifty-one years, a case of Dr. B. S. Barringer, had had diabetes about twelve years. By using moderate restriction of diet he had maintained good health and had not been restricted in his activities. Early in 1923, he developed symptoms which resulted in his consulting a genito-urinary surgeon. Cystopic examination revealed a malignant papilloma of the bladder which was treated with radium. Following this treatment there was retention of urine and an excessive irritability of the bladder necessitating frequent catheterizations—for a period, every two hours, day and night. It seemed desirable to give attention to the diabetes in order to reduce the urine volume primarily and also to improve the patient's condition sufficiently to permit completion of the urological treatment.

At this time the patient seemed to present a problem of no unusual difficulty. He was weak and emaciated but there was no evidence of significant infection. The temperature, pulse and respirations were normal. The urine volume averaged about 2 liters and contained 80 to 90 gm. of glucose; there was a moderate

acetone reaction, but none with ferric chloride. The blood sugar was 250 mg. per cent, which seemed at the time moderate in degree. Nephritis was suspected but no supporting evidence was secured; the urea nitrogen of the blood was 13.8 mg. per cent. The patient was given a diet containing 1800 calories and 75 gm. of carbohydrate and iletin treatment was started with a dose of 45 units per day. He was encouraged to drink as much water as possible.

The following day there had been no abatement of the glycosuria and since the iletin dosage seemed too large to continue with only a moderate elevation of blood sugar, it was given in 5-unit doses every two hours and each voiding of urine (catheterization) tested for sugar. Fifty units were given without detectable effect during the day. The patient seemed very weak and intoxicated but did not then impress me as suffering from acidosis. The morning of the third day he was definitely worse. He was rather drowsy, the respiratory rate had increased to 40 and the tongue was dry. The patient had no appetite and the diet was discontinued. He was given as much orange juice as he would take and a liter of milk. A solution of 5 per cent glucose and 3 per cent soda bicarbonate was injected by the Murphy drip method at intervals. During this day about 1800 cc of water was given intravenously and subcutaneously. Alkalies were administered in the intravenous solutions and by mouth. Twenty units of iletin were given at ten o'clock and the same dose intravenously at eleven; 10 unit doses were given every two hours till nine o'clock in the evening; a total of 110 units during the day. There was no abatement in the intensity of the glycosuria; ketone bodies were still present but the reaction with ferric chloride was faint. The patient was evidently becoming worse rapidly in spite of all that could be done. The pulse was weak and cardiac failure being feared, caffeine was used intravenously. The same measures were continued till death occurred six hours later. The patient did not develop a typical coma. There was stupor but until an hour or two before death he could be roused. The respirations were at times 40 per minute but for some hours prior to death were 30 and were not characteristic though suggestive of acidosis. The temperature was normal. In the absence of necessary analyses of the blood I am uncertain whether this patient died of diabetic acidosis or some unrecognized complication. It is the only case I have seen in which iletin treatment produced no definite effect upon the glycosuria.

[We are glad to acknowledge indebtedness to the Eli Lilly Company for supplies of iletin (insulin Lilly) which were furnished gratis during the experimental period of its use.]



## ILEOCECAL INCOMPETENCE. A CLINICAL ANALYSIS OF 1000 CASES WITH SOME DEDUCTIONS THEREFROM.\*

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INCOMPETENCE of the ileocecal valve as a cause of subjective symptoms has been a matter for controversial discussion for a number of years. The varying views have ranged from a dogmatic denial of all significance and the assumption that all persons have a variable degree of ileocecal regurgitation<sup>1</sup> to the other extreme that the finding of this condition in a medically irrelievable degree may be a fit indication for surgical interference.<sup>2</sup> Because of these varying views and also because of the general indifference to, and lack of present-day knowledge of, motor disturbances of the gastro-intestinal tract, we have recorded as carefully as possible all roentgenological abdominal data with the view of analyzing it in relation to this condition, when we had accumulated a sufficiently large number of cases to make such a study worth while.†

Regurgitation through the ileocecal valve has been known for a long time. Cannon, Keith, Elliott<sup>3</sup> and others have studied it experimentally. Cunningham<sup>4</sup> has described anatomical variations in the structure of the valve. Case<sup>5</sup> first found the condition roentgenologically in 1910, and this was verified and acknowledged soon afterward in Europe by Schwartz, Holzknecht and Singer<sup>6</sup> of Vienna and others.

It soon became the opinion of many different roentgenologists and clinicians<sup>7</sup> that incompetency of the valve was a very frequent condition and that the former of the two above mentioned views was incorrect. It has been, therefore, with the idea of attempting to see if some general conclusions might be formulated that this study was undertaken; whether local or general symptoms might

\* The following clinical analysis of gastro-intestinal patients presenting a variable degree of ileocecal incompetence was made during the years 1914 to 1919, and the present paper was in most part written during that period. During the past four years these observations have been carefully weighed in the study of further material and the result of this added experience together with the longer observation of many of the older patients justifies us in presenting our conclusions as they were formed at that time. Naturally, but few miscellaneous reports on the subject appeared during the period of the war, although previous to it a number of controversial papers were written and an unjust amount of adverse criticism was expressed. Recently, Bryant of Boston, has again emphasized the necessity of placing some clinical significance upon the presence of ileal regurgitation in persons suffering with chronic gastro-intestinal symptoms, an effort that is wholly in accord with our experience.

† In a recent personal communication from Dr. Kellogg, he writes me that he has operated upon only 2 patients for ileocecal regurgitation without the coexistence of some distinct surgical lesion within the abdomen, and then only after the complete failure of medical control.

be referred to the presence of regurgitation; whether or not these symptoms could be removed by a medical or dietetic plan of bowel regulation; and also, if possible, to judge whether surgery should ever be entertained even in those cases in which symptomatic relief is not given by medical means and the patient distinctly suffers. The diagnosis of the so-called border-line abdominal diseases, into which problem motor disturbances of the gastro-intestinal tract enter so prominently, may never reach that degree of perfection where one may always say with positiveness, for instance, that a latent gall-bladder disease does or does not exist. To the surgical mind it may always be justifiable to explore the abdomen in an effort to find the cause of symptoms, but the trouble lies in the fact that many cases are explored surgically without relief to the patient or increased knowledge to the surgeon, who then dismisses the matter with the general diagnosis of neurasthenia. In the year 1915, roughly 70 per cent of our hospital patients suffering from gastro-intestinal symptoms had already been operated upon for supposed chronic appendicitis or some assumed pelvic disturbance without the relief of their symptoms. So many patients with such histories continue to be seen that it is quite justifiable to say that these mistaken diagnoses are being made quite generally today. The end-results of patients of this group treated medically after they had been operated upon for either actual or fancied surgical conditions within the abdomen justifies one in the belief that the symptoms were originally due to motor disturbances of the gastro-intestinal tract, often in association with a general asthenic state.

The clinical analysis of any large group of cases, without a determined pathological basis, especially when a number of years had elapsed during its accumulation, is open to evident criticism. This may be due to many things; changing interpretation of the same clinical findings, changing technic, the influence of advancement made in related fields, as, for instance, the bearing which the newly acquired knowledge of the physiology of the gastro-intestinal tract has upon this particular group of cases, etc. Personal bias may in a measure be eliminated by having different workers pass upon the interpretations. The roentgenological data of this group have been obtained in this manner. Where possible the cataloguing has been done by nurse assistants. In other words, an attempt has been made to rule out gross errors. One may say, furthermore, that the majority of the cases making up this group are instances of motor disturbances of the gastro-intestinal tract. It is not probable that a large percentage had unrecognized local lesions, such as gall-bladder and appendix affections or duodenal ulcer, for, in case of any doubt, these have been excluded. Neither should one assume that all of the symptoms experienced by these patients have been due to an ileocecal regurgitation. Rather have we

looked upon the incompetence as a factor, more or less marked in different cases in a general gastro-intestinal motor disturbance—more often a minor factor. Therefore, these cases in general represent a group of chronic gastro-intestinal patients, who, for the most part, have sought relief from gastro-intestinal symptoms. They have been tabulated for the reason that in the course of their examinations a variable amount of ileocecal regurgitation has been encountered, and local abdominal lesions, aside from pericolic bands, could reasonably be excluded.

TABLE I.—SEX AND AGE INCIDENCE IN 500 CASES OF ILEOCECAL INCOMPETENCE.

Degree of incompetence.	No. of cases.	Male.	Female.	Age.					
				1 to 20	20 to 30	30 to 40	40 to 50	50 to 60	60 and over.
+	359	143	216	10	87	126	70	55	19
++	106	34	72	2	17	40	24	19	5
+++	35	8	27	..	5	17	4	8	1
Totals	500	185	315	12	109	183	98	82	25

In Tables I and II, the first 500 cases have been analyzed more in detail. In the course of this analysis there has been noted a strikingly large percentage of patients of the general asthenic type of build and with right colons loosely fixed in the abdomen, usually in conjunction with mobile cecums. For this reason a larger number, namely, 1000 cases have been analyzed to determine the incidence of mobile cecum to ileocecal regurgitation, and these figures are given separately in Table III.

The important point noted in Table I, if we can ascribe any causative relation between ileocecal regurgitation and a loosely fixed right colon, is the preponderance of females having a regurgitation, namely, 315 to 185. Wolkow and Delitzin<sup>8</sup> in 1899, by means of sections and plaster-of-Paris casts, showed that the structure and configuration of the female pelvis was conducive to a ptosis especially of the right kidney and a lack of proper rotation and fixation of the right colon. Later this was varified by Coffey<sup>9</sup> by means of cast work.

The more detailed analysis of symptoms in Table II gives prominence to pain, gas, constipation and the so-called toxic symptoms. A twelve-hour ileum stasis occurred 204 times and 97 had undergone appendix or pelvic operations, roughly 20 per cent. According to the patient's histories, seemingly most of these operations were undertaken because of the presenee of abdominal distress. In regard to a possible underlying chemical cause for the so-called

TABLE II.—SYMPTOMS NOTED IN 500 CASES OF ILEOCECAL INCOMPETENCE.

Degree of incompetence	No. of cases.	Gas.	Pain.	Nausea.	Vomit.	Constip.	Dysen.	Alter.	Toxic symp-toms.	Gen. asth.	Achylin.	Stasis.		Duo. drag.	Mucous colitis.	Epileptoid attacks.	Appen-dec-tomy.	Pelvic opera-tions.
												Il.	Duo.					
+	359	227	196	59	41	256	20	9	274	161	17	159	63	18	12	2	47	16
++	106	73	64	25	19	73	4	2	89	46	10	36	15	7	4	1	14	12
+++	35	29	21	8	6	28	1	..	26	12	2	9	5	2	3	..	3	5
Totals	500	329	281	92	66	357	25	11	389	219	29	204	83	27	19	3	64	33

toxic symptoms—dulness, languor, dull headache, despondency, etc.—as Mutch<sup>10</sup> believes there to be, we can add nothing except our clinical data. The opposing work of Mellanby<sup>11</sup> and others, and the deducted views of Alvarez<sup>12</sup> are not conclusive to us, for we have seen clinically examples of chronic diarrhea due entirely, it would seem, to an ileal stasis and regurgitation, accompanied by marked depression, languor, etc., disappear entirely by dietetic measures, with the relief of the stasis. Likewise, the chronic constipation case, No. 4254, detailed below, is difficult to understand except from the standpoint of a chemical poisoning. It is to be noted that, roughly, 70 per cent of the cases complained of these toxic symptoms.

TABLE III.—A REPORT OF 1000 CASES SHOWING RELATION OF MOBILE CECUM TO ILEOCECAL INCOMPETENCE.

Degree of incompetence.	Total.	Mobile cecum.	Fixed cecum.	Per cent Mobile cecum.
+ and ++ . . . . .	695	556	139	80.0
+++ . . . . .	232	212	20	91.3
++++ . . . . .	73	65	8	89.0
	1000	833	167	83.3

Table III details the most striking and the most interesting feature of the group analysis; namely, the very high percentage of mobile cecum found in patients having ileocecal incompetence. The interpretation of mobile cecum roentgenologically is open to criticism for it must necessarily be an arbitrary one. Our associates, Drs. Palmer, Payne and Trahar, have arbitrarily designated a mobile cecum as one which can be moved vertically upward from  $3\frac{1}{2}$  to 4 inches or more, as shown by comparative screen examinations in the upright position and colon enema examinations in the prone position. The cases also in which the cecum lies low in the pelvis and cannot for any reason be raised, and where there is an accompanying asthenic build with right kidney and stomach ptosis, have been likewise included in this group. The degree of mobile cecum, as also the degree of ileocecal incompetence, has been arbitrarily designated as 1+, 2+, 3+ and 4+. In extenuation of this way of determining a mobile cecum, we may say that very few patients in whom such findings have been made and who have come to abdominal operation for any reason, have failed to show a more or less movable cecum. The majority of these patients have also shown a right colon suspended by its own mesocolon, which in turn has not, in its development, become attached to the kidney shelf but hangs from a position near the mid-vertical line.

With 83.3 per cent of the 1000 cases showing a determinable degree of cecum mobility, one must believe that more than an accidental relationship exists between the two. In fact in the majority of the irrelievable cecum stasis cases which have come to operation the most important operative point in obtaining relief of symptoms has been the proper placement of the right colon on the kidney shelf. Some of these patients have not shown accessory bands, so that local pain and tenderness is not to be explained in them by traction upon such bands.\* Again, and this is of the utmost importance, such individuals who have failed to respond to reconstructive methods and have remained weak and so-called neurasthenics, have found that their colons could be easily regulated, their bodies redeveloped and their asthenic and neurasthenic states overcome after the right colon had been so placed in the right paravertebral niche. These colons have appeared clinically as though the absence of this fixed point of purchase against which the musculature of the bowel may pull was the principal factor involved. That means that in these individuals it would appear clinically as though this factor was able to offset the peristaltic gradients, the influence of intra-abdominal pressure, the support of the anterior abdominal wall, the type of the bowel content, etc., combined. As will be seen below, this point has entered into a certain number of the cases placed in this group as having ileocecal incompetence.

The details of the findings in 20 ordinarily healthy persons who had no constipation, abdominal distress or toxic symptoms are given in Table IV. It so happens that out of 6 cases showing five, 2+ and one, 3+ ileocecal regurgitation, 5 of these had mobile cecums, or 83.3 per cent. Of the 10 cases of regurgitation of all degrees 6 had mobile cecums, or 60 per cent. These examinations were made in 1917. It is of greater interest to learn that one year later, following a light attack of influenza, Case No. 13, an asthenic built but very strong girl, who showed originally a mobile cecum, ileum stasis and a 3+ regurgitation, developed a marked general asthenia with constipation and attacks of pain and local tenderness in the right lower abdominal quadrant, which continued for

\* Case: Discussing the relation of ring constriction waves in the cecum to cecal stasis, says: "When these ring constrictions . . . persistently fail to empty the tip of the cecum, it may be inferred that the cecum is fixed by adhesions, frequently associated with appendix disease. This finding suggests that it is the fixed rather than the freely movable cecum which is likely to give rise to stasis, and it would indicate that undue importance has been attached to the condition known as mobile cecum; that adhesions and fixation of the cecum are likely to give rise to evil consequences rather than mobility, and that harm rather than good may be done by operations for fixation of the cecum." It is true that the majority of cecum stasis cases are seen at operation to have associated pericolic bands, but we have the records of a number of cases of mobile cecum with irrelievable cecum stasis, constant tenderness and periodic attacks of pain in which no adhesions and no appendix disease were found at operation and which now show good postoperative end-results.

several months. These symptoms and the general asthenia were later overcome in a dietetic and reconstructive manner.

TABLE IV.—INCIDENCE OF ILEOCECAL INCOMPETENCE IN 20 HEALTHY PEOPLE.

		M.	F.	Age.	Type.	Mobile cecum.	Ileum stasis.	Regurgitation.
1	F.	..	+	33	Asth.	+++	○	+
2	R.	..	+	18	Sth	○	○○	++
3	L.	..	+	18	Sth	+	○○	++
4	J. a.	+	..	50	Sth	+	○	○
5	J. b.	..	+	14	Sth	○	+	○
6	J. c.	+	..	10	Sth	○	○	○
7	K.	..	+	28	Sth	+	○	○
8	C.	..	+	32	Asth.	+++	○	○
9	Fa	..	+	24	Asth.	++	○	++
10	T.	..	+	28	Asth.	++	+	++
11	H.	..	+	20	Sth	+	○	++
12	Mc	+	..	56	Sth	○	+	+
13	Mc 2	..	+	18	Asth.	+++	++	+++
14	B.	..	+	19	Sth	○	+++	+
15	Tr.	+	..	45	Sth	○	○	+
16	P.	+	..	32	Sth	○	○	○
17	J. 1	+	..	42	Sth	○	○	○
18	J. 2	..	+	36	Sth	○	○	○
19	J. 3	+	..	8	Sth	○	○	○
20	J. 4	+	..	5	Sth	○	○	○
Totals		8	12			9	5	10

In 6 cases of 2+ and 3+ ileocecal incompetence 5 cases or 83.3 per cent showed mobile cecum.

Several roentgenologists have expressed informally the opinion that all normal ileocecal valves could be made incompetent if a barium enema were allowed to remain in the colon a sufficient length of time. To test these statements we have held 10 patients, who at their first examination had shown no ileocecal regurgitation, under observation for one hour, with the results shown in Table V. These results indicate that the ileocecal valve may at times be fully competent for the duration of one hour, even in the presence of a mobile cecum and distinct motor disturbance of the gastrointestinal tract. The first and second examinations were always made on different days.

**Illustrative Case Records.** In the study of the cases, varying conditions and varying responses to treatment have been met. One may easily separate them into groups according to their response to treatment and the methods of treatment employed. Behind them all, it would seem to us, lies the fundamental principle of maintaining a regulated gradient of intestinal forces, as will be mentioned later. There were patients who received symptomatic

relief from dietetic and physical reconstruction methods, both with the removal of the ileocecal regurgitation and without its removal. There were others who were treated surgically, both with and without relief; and also 1 case of partial colectomy and 1 case of Lane's short-circuit operation have been appended because each showed the greatest possible degree of ileal stasis and regurgitation with symptomatic relief from medical measures, although such cases have not been included in the list of 1000.

TABLE V.—ILEOCECAL COMPETENCY AS SHOWN BY 10 PATIENTS UNDER OBSERVATION FOR ONE HOUR.

Case No.	Diagnosis.	1st examination.		2d examination. Minutes.			
			0	15'	30'	45'	60'
A 14964	Chr. gall-bladder; periduodenal bands, colon stasis, mobile cecum +	○	tr.	—	+	—	tr.
A 18538	Gen. asthenia, colon stasis, mobile cecum 2 +	○	○	○	○	○	○
A 18746	Gen. asthenia and ptotic mobile cecum +	○	+	—	—	tr.	++
A 18615	Gen. asthenia and ptotic, cecal and colon stasis, mobile cecum 3 +	○	○	○	○	○	○
A 18774	Chr. gall-bladder; ileum and colon stasis, mobile cecum +	○	○	tr.	○	○	○
A 19374	Dental sepsis, gastro-intestinal sequelæ, mobile cecum ○	○	○	tr.	○	○	○
			0'	20'	40'	60'	
B 258	Sinus infection, chr. appendicitis and local peritonitis, mobile cecum ○	○	tr.	○	—	tr.	
B 566	Gen. asthenia and ptotic, colon stasis, mobile cecum +	○	○	○	tr.	—	
B 595	Ext. gen. asth., colon stasis, mobile cecum 2 +	○	○	○	○	○	
B 73	Post influenzal gen. asth., ptotic, colon stasis, mobile cecum 3 +	○	○	○	○	○	

The cases have been grouped, therefore, in the following manner, and under each heading a few briefly detailed illustrative case records are given to emphasize the points in question.

GROUP I. Those cases which responded to medical treatment with satisfactory symptomatic relief.

GROUP II. Those cases which failed to respond to medical treatment and did not come to operation.



GROUP III. Surgically treated cases into the symptom complex of which entered the question of ileocecal regurgitation.

(a) Medically irrelievable cases associated with mobile cecum.

(b) Medically irrelievable, uncomplicated ileocecal regurgitation.

And also:

(c) Partial colectomy, without relief of symptoms.

(d) Lane short circuit operation, without relief of symptoms.

GROUP I. *Those cases which responded to medical treatment with satisfactory symptomatic relief.*

Medical Case No. 6327, November 17, 1915. A woman, aged twenty-four years, married, nullipara; of moderate asthenic type of build with movable cecum, was always in good health until the beginning of her present illness. In June, 1914, the patient suffered an acute attack of appendicitis with rupture. Appendectomy was performed and the patient recovered from the effects of the acute illness and operation. In September of the same year there began nausea, stomach distress, and vomiting usually taking place in the evening following dinner. The bowel remained regular except for slight periods of looseness and considerable gas and bloating that was relieved by the passing of flatus. Physical examination of the patient was negative throughout with the exception of a tender, spastic cecum and colon. A 4+ ileocecal regurgitation was present. Response to the principles of bowel regulation was prompt with complete relief of symptoms, which condition has remained to date, seven years later. This patient had been frequently urged to submit to further surgery for the relief of adhesions.

Medical Case No. 13184, May, 1919. A female, aged thirty-four years, para I, of moderate, squatty type of build with slight postural scoliosis was in good health until the beginning of her present trouble eight years ago. The patient then became distressed with an irregularly recurring drawing pain in the stomach which was relieved by lying down, the applying of heat, or by eating. Following the taking of food the pain would again recur in two hours. There was no belching, nausea or vomiting. At the same time pain occurred in the right side of the abdomen, of a dull nature, with local soreness but never accompanied by fever, nausea or vomiting. During the period of the distress the patient could not lie on the right side because of this pain. The bowel had moved regularly for the most part with occasional periods of slight looseness with shreds of mucus. General physical examination revealed normal findings with the exception of a 4+ ileo-

cecal regurgitation and a 1+ twelve-hour ileum stasis. The patient responded quickly to the principles of bowel regulation and obtained definite relief of all symptoms together with nearly a complete removal of the ileocecal regurgitation. This patient has had the diagnosis of chronic appendicitis made repeatedly and advised to be operated upon for it.

Medical Case No. 6292, February, 1916, a male, aged forty-six years, of heavy, squatty type of build, was always of robust health. For the past twenty-five years the patient has had irregular periods of dizziness, fever, sweating and chilliness associated with gas, belching and looseness of the bowel; the so-called toxic symptoms being very marked and always accompanied with much nervousness and psychical depression; never did he suffer pain, nor was the bowel ever constipated. General physical examination between these periods of distress revealed normal findings throughout. During the period of attacks ileocecal regurgitation alone was determined. These attacks seemingly recurred whenever the patient left his routine habits of living. Frequently they would appear while he was in camp on fishing or hunting trips, and during a period of three years he would place himself under rigid dietetic control for a short time in order to overcome these symptoms. At no time was there any suggestion of other pathology found in the numerous examinations made upon him. It was often believed that a hidden gall-bladder disease existed to explain his recurring attacks. In January, 1919, the patient died with the picture of an acute infection characterized by an onset similar to the above mentioned attacks, which rapidly passed into a state accompanied by increasing urinary suppression, a toxic jaundice, increasing pulmonary edema, and on the day preceding death, auricular fibrillation. Autopsy performed a few hours after death revealed a small area of bronchopneumonia at the base of the right lung with gray hepatization, but no other strictly local lesions. The gall-bladder and appendix were normal. The ileocecal valve appeared entirely normal in its anatomical structure. Death probably was due to an acute influenzal infection which was masked by symptoms first referred to the kidney and liver. No further explanation for the occurrence of the patient's periodic attacks during life was obtained, so we were forced back to the assumption that his recurring illnesses were in some way associated with his periodic ileocecal regurgitation.

Medical Case No. 3598, June, 1916. A male, aged forty-eight years, heavy, squatty type of build, was always in robust health until the beginning of the present trouble. Four years ago the patient began to have irregular bowel movements with tendency to diarrhea. Frequently a loose stool was passed immediately

after eating, and occasionally constipation existed. About eight weeks ago the patient was seized with severe pain in the lower right abdominal quadrant, without fever but with nausea and vomiting. No local soreness existed. The attack lasted two or three days. A second similar attack occurred three days preceding date of examination. There was a sharp, colicky pain in the region of the appendix, which was promptly relieved by using a warm water flushing. There was but little soreness or gas. General toxic symptoms consisting of dulness, languor, dull headaches together with mild muscle and joint pains had existed throughout the preceding four years. At this time our physical examination revealed normal findings with the exception of dental sepsis and a marked ileocecal regurgitation. Under the principles of dietetic bowel regulation and the removal of several abscessed teeth, the symptoms promptly cleared. Most striking was the relief of the feeling of languor and depression, the patient's head became more clear and he went about his work, that of a travelling salesman, with much more spirit and ambition. A few months later, while in the Middle East, he suffered a third attack of pain in the right lower abdominal quadrant, at which time a calculus was located in the right ureter and removed by operation. Following the operation the patient's former looseness of the bowel returned together with the old symptoms of mental depression, dull headaches, with his former lack of power of concentration. This continued until he again consulted us in March, 1918, at which time a marked degree of ileocecal regurgitation was again found. Again he responded to dietetic bowel regulation with the relief of the symptoms, and at the time of the last report, one year ago, the patient was feeling entirely well by following this regimen.

GROUP II. *Those cases which fail to respond to medical treatment and did not come to operation.*

Medical Case No. 6916, February, 1917. A female, aged thirty-four years, para II, heavy, squatty type of build, she had always been physically strong and well with the exception of severe headaches which began in childhood. Fourteen years ago there began constipation, a cathartic habit, gas, bloating, belching, colic pains throughout the bowel, much soreness along the line of the colon together with continued headaches and marked toxic symptoms. The patient felt dull, stupid, dizzy, sleepy, with cold hands and feet, and was excessively nervous. These symptoms have continued irregularly but constantly for the past fourteen years. Physical examination revealed normal findings with the exception of a tender, spastic colon. Moderate duodenal lagging and very marked ileocecal regurgitation were noted. The cecum and ascending colon appeared normally fixed upon the kidney shelf. For a

period of three weeks this patient was under control in the hospital without relief of her symptoms and without obtaining a dietetic regulation of the bowel. Abdominal exploration was not accepted, and the patient continued at last account with the same degree of symptoms. Without more exact information it has been assumed that this patient is suffering with an irrelievable type of ileocecal incompetency.

GROUP III. *The remaining case histories illustrate different types of surgically treated cases, into the symptom complex of which entered the question of ileocecal regurgitation.*

*A. Medically Irrelievable Cases Associated with Mobile Cecum.*  
—Medical Case No. 7394, April, 1917. A female, aged twenty years, single, of a general asthenic type of build, was in moderately good health until three years ago. At that time she became run-down, lost weight and strength, and especially for the past year and a half has suffered much physical and psychical depression and bodily weakness. Since the preceding November she has suffered from severe shooting pains in the stomach, appearing immediately after eating, these passing straight through to the back and under the left shoulder blade. Nausea and vomiting following breakfast have occurred nearly every day since the onset, but is relieved during the latter part of the day, when the patient is able to retain most of her meal. Much burning in the stomach is experienced at night. There has never been constipation, but during the past year and a half she frequently has had periods of looseness of the bowel with gas and griping pain. She has also suffered constant aching and a dragging sensation in the small of the back while standing or walking, and frequently recurring headaches. The general physical examination was that of a tall, generally undernourished, asthenically built girl, a straight back type with a moderate postural scoliosis. The roentgen-ray examination of the abdomen showed a midline gastropnoxis, freely movable cecum and ascending colon, duodenal drag with lagging in the second portion, and a filling defect in the bulb, seemingly due to periduodenal bands; duodenal tenderness and a marked degree of ileocecal regurgitation. No relief was obtained in hospital by medical treatment during a period of three weeks. The operation revealed no further pathology. One acquired band extended from the duodenum to the transverse colon; a second band attached the colon to the parietal peritoneum. The operation consisted of appendectomy, plication of the cecum and the fixation of the right colon on the kidney shelf. After a period of four weeks the patient was returned to the Medical Hospital, where the general process of reconstructing the extreme general asthenic type of body build was instituted with the result that the patient has obtained a good degree of health and strength.

Medical Case No. 7268, April, 1917. A female, aged forty-one years, para I, of moderately squatty type of build, was in good health until seventeen years of age when there began symptoms of what was diagnosed as chronic appendicitis. Five years ago an appendectomy was done since which time the patient has never been well. At the time of her first illness there began cramping pains along the course of the colon, periodic nausea and vomiting, constipation with alternating dysentery, much mucus in clumps and strings in the stools, abdominal soreness, rheumatic muscle pains, and extreme nervousness. This has occurred in varying degree up to the present time. Physical examination revealed in the main normal findings; the colon was spastic and tender; the stools contained much mucus. Roentgen-ray examination of the abdomen showed marked duodenal stasis, 2+ twelve-hour ileum stasis, a marked degree of ileocecal regurgitation, mobile cecum, and a generally spastic colon. Effort in hospital, under control, to relieve the symptoms and regulate the bowel proved futile, and she was operated upon with the following operative findings: Cyst on the right ovary the size of a hen's egg, incompetent ileocecal valve, large dilated and flabby cecum which was entirely mobile, long mesentery which permitted the entire right colon and hepatic flexure being turned well out through the wound. The operation consisted of enucleation of the cystic portion of the ovary, repair of the ileocecal valve (modified Kellogg operation), plication of the cecum, and the fixation of the right colon. The patient believing that the surgical operation should relieve her of her symptoms, refused to submit to dietetic measures following it and went home without relief. A couple of months later her distress remaining as severe as before her operation, she submitted to dietetic control and was relieved in large measure of her abdominal pain and distress; the stools became regular and quite free from mucus. Later, believing herself quite well, she ignored her dietetic regimen with the result that she was soon back to the condition in which she had been for so many years. A little persuasion, however, induced her to return to a mechanically fine, bland diet, which she has since followed with definite satisfaction.

*B. Medically Irrelievable, Uncomplicated Ileocecal Incompetence Cases.*—Medical Case No. 4254, July, 1914. A male, aged thirty-two years, of gaunt, asthenic type of build. At the age of seven the patient began to have what was termed bilious attacks; a dull, occipital pain extending over the head back of the eyes, coming on at irregular times of the day and recurring at weekly to monthly intervals. In 1903, he became very nervous, irritable, irrational and suffered much from insomnia. He complained of the so-called toxic symptoms very markedly, with entire lack of concentration and ability to work. He was considered for some years mentally

unbalanced by his neighbors and the members of his own family. When first seen, in 1914, his physical examination revealed septic tonsils and a moderate degree of pyorrhea, a sallow, pigmented skin, a general abdominal ptosis of moderate degree, and normal stomach, blood and urine chemistry. Roentgen-ray examination revealed normal findings with the exception of a 4+ ileocecal regurgitation. The cecum and ascending colon seemingly were normally fixed upon the kidney shelf. For a period of one and a half years this patient was under more or less constant medical control both in and out of hospital. His septic tonsils and dental sepsis were removed; a moderate grade of ethmoid sinusitis treated, and an attempt was made to overcome his general so-called toxic symptoms by means of bowel regulation and the principles of body reconstruction, but only a moderate degree of success was obtained. At no time was the patient relieved of his feeling of mental depression, his headaches, his lack of interest and ambition. In May, 1915, an exploratory abdominal operation was performed and nothing but an ileocecal valve incompetence determined. Pericolic bands were removed and the Kellogg operation for incompetent ileocecal valve was performed. The day following operation, while visiting the patient, he described his condition as though a load had been lifted from his head. He stated that not for years had his head felt so clear and free from headache as it did that morning. He made a rapid convalescence and returned home feeling better than he had for years. He picked up in weight and strength rapidly and went to work on the farm. He felt very well for about nine months, when he returned with the statement that two or three weeks before he had begun to experience the same feeling of depression and head symptoms which he had had previous to his operation. Barium enemas again showed the presence of marked ileocecal regurgitation. He again asked to have the operation of closing the ileocecal valve repeated, but not believing it to be justifiable at the time, the patient was again placed upon the principles of rigid bowel regulation, forced feeding and physical gymnastics. During the succeeding years repeated barium enemas have been given, with the result that a marked degree of ileocecal regurgitation has always been found. On June 23, 1919, the following note was recorded on his history: "Patient's head has felt clear for the past two years; periodically, possibly once a week, he feels a hurting and tenderness about the region of the cecum—a feeling of blocking, although the bowel moves well each day. His general health has been improved; has continued his work on the farm without interruption." On this day a 4+ ileocecal regurgitation was again found by roentgen ray.

Medical Case No. 5175, February, 1916. A business man, aged thirty-three years, of gaunt, asthenic type of build, whose

general health was good until 1895, when distress began in the stomach, one to two hours after eating, associated with gas and an obstinate constipation. A cathartic and enema habit soon followed. The patient became nervous, apprehensive, lost in weight and strength and developed headaches. The general physical examination revealed normal findings. Roentgen-ray examination of the abdomen showed only a marked ileocecal regurgitation. In hospital, under control, it was found impossible to regulate the bowel or to relieve the patient's symptoms. In July, 1916, the abdomen was explored with the preoperative diagnosis of incompetent ileocecal valve and a possible gall-bladder infection because of suspicious shadows in gall-bladder films. The operative findings were adhesions folding the appendix on itself and attaching it to the parietal peritoneum; incompetent ileocecal valve; ascending colon normally fused; gall-bladder, stomach and other abdominal organs normal. The operation consisted of removing the appendix and repairing the ileocecal valve by the Kellogg method. Immediately following the operation very decided relief of the patient's head symptoms, together with the easy regulation of his bowel, was obtained. Later he had a return of his symptoms, but he has always been able to offset them by dietetic means, and his general health is much improved. We have never been able to reexamine his intestinal tract by the roentgen ray since the return of his distress, but it is our belief that he has an ileocecal incompetency and that he is obtaining symptomatic relief by his bowel regulation.

*C. Partial Colectomy Without Relief of Symptoms.*—Medical Case No. 6511, December, 1916. A female, aged thirty-five years, para I, of general asthenic type of build, was never strong and always constipated from childhood. The patient's history is that of a severe general asthenic and ptotic individual with obstinate constipation with its usual train of accompanying symptoms. In February, 1916, a partial colectomy was performed for relief of her obstinate constipation in the Middle East by the Bloodgood method. Following the operation she had relief for about six months. Then the symptoms returned together with much pain, colic, gas and periodic loose stools. She rapidly lost in weight and strength again and her general health has been poor. An examination revealed a very asthenic, moderately straight back type of body build, pigmented skin, thin, emaciated abdominal wall with active peristalsis in the coils of the bowel visible through it. The new anastomosis of the ileum to the transverse colon together with a marked midline ptosis of the stomach, a twelve-hour stomach stasis, a duodenal drag, and a widely dilated terminal ileum with constant stasis was shown roentgenologically. Under control in hospital, it was found that the loose bowel movements could be overcome, the pain and sore-

ness and gas were relieved by dietetic measures, and the patient made very good progress toward rebuilding her general asthenic state. After six weeks in the hospital she returned home and continued to be well until the following fall, when the work and worry incident to taking care of a sick child again upset her bowel and was followed by a rapid loss of weight and strength and recurrence of her former symptoms. She returned to the hospital, was again reregulated and sent back home in very good health. For the third time she returned in the spring of 1919 with a moderate recurrence of her former symptoms. At this time a more complete carrying out of the reconstruction principles incident to her bowel regulation and her general asthenic type of build was done, and the patient returned home believing that she would then be able to maintain permanently a good degree of body health. At all times has there been present, both during her periods of physical weakness and bowel irregularity and during her periods of comparative good health, a marked degree of ileal regurgitation and dilatation.

*D. Lane Short-circuit Operation, with Persistent Symptoms.*—Medical Case No. 7439, May, 1917. A female aged forty-three, years, para II, of moderately asthenic type of build, had fairly good health in childhood and until eleven years ago when she was operated upon for a tuberculous peritonitis. Following this operation she became quite well, but six years ago a Lane short-circuit operation was done because of an obstruction of the bowel, as related by the patient herself. Following this operation she was again fairly well until two years ago when there began periods of pain, gas, bloating and vomiting, with acute attacks of severe looseness of the bowel, lasting about twelve hours each. With these recurring attacks the patient lost rapidly in weight and strength. This condition has continued until the present time. General examinations have shown in the main normal findings. Roentgen-ray examination of the gastro-intestinal tract showed clearly the ileosigmoidostomy and the large dilated ileum with its persistent stasis. The entire colon would fill with barium to the cecum where it would remain lodged for days. It was found on attempting to regulate the bowel that it was possible to overcome the gas and pain and periodic dysentery, to the end that the stools became regular and formed. The patient put on weight, gained in strength quite rapidly, and after six weeks in the hospital returned home very much improved in health. A year later she returned with a recurrence of the former symptoms. These were again quickly set aside and she returned home to continue for all times a rigid dietetic bowel control. Repeated examinations, both during the time of her illness and afterward, showed the same permanently dilated ileum with its persistent stasis. In spite of this condition the patient remains very well and strong.



Since the compilation of the above records was finished in 1919, 2 more patients suffering with an irrelievable ileocecal regurgitation and cecal stasis with mobile cecum have come to operation. In these 2 cases only the fixation of the right colon and cecum was done and no repair of the ileocecal valve was made because our experience with the previous ones had made us believe that in the cases in which there was a definite right-sided colon ptosis the important principle in the surgical treatment was the fixation upon the kidney shelf of the loosely attached bowel. Leaving the valve unrepaired in any way and noting the medical result after the operation would give one added evidence as to the correctness of the opinion that it was the influence of the added mechanical support of the fixation which actually permitted the cecum to empty itself, and gave to the patient relief from his symptoms. Both of these patients worked out in this way.

Medical Case No. 10897. A female, single, aged nineteen years, was first seen in 1918. The patient was of an extreme asthenic type of build, and never had been strong; she had suffered from constipation and so-called bilious spells more or less all her life. For the past three years she has suffered more from increasing weakness, nervousness, irregular pains after eating, colic distress through the bowel and frequent throbbing, dizzy frontal headaches with much nausea but no vomiting. Her examination showed an extremely asthenic, sway-back type of body build with marked postural scoliosis, a general abdominal ptosis, a dilated cecum lying low in the pelvis with a 3+ ileocecal regurgitation, but otherwise normal findings. For three weeks the patient was under control in hospital without relief from the cecal stasis or abdominal distress. Abdominal exploration was advised and was refused. In April, 1919, she was operated upon elsewhere for chronic appendicitis without relief of symptoms and with an increasing amount general body weakness and functional nervousness. In November, 1920, she returned to us and was again tested out in hospital with the same results as before. The patient had lost much in weight and strength and had become a profound neurasthenic. In spite of this condition we advised surgical relief and this was done November 22d. A marked right colon ptosis with a large dilated mobile cecum lying free in the pelvis was all that was found. There were no pericolic bands present about the bowel. A right colon fixation operation was done together with a plication of the cecum. The patient's convalescence was prolonged and very stormy because of an accompanying psychic imbalance which set in soon after operation and from which the patient has not yet fully recovered. The effect upon the bowel function, however, was very prompt. Complete regulation of the bowel was easily obtained, and the patient added weight easily, although strength more slowly. She

was last examined in January, 1922, and the bowel was found to be functioning normally. The presence or absence of ileocecal regurgitation was not determined. Her physical health is very good; psychically she is still upset although she is slowly working out this problem satisfactorily.

Medical Case No. 17954. A female, single, aged eighteen years, was first studied in December, 1920. The patient complained of much gas, bloating and colicky pains through the bowel. At times persistent diarrhea would occur together with nausea and uncontrollable vomiting, shortness of breath and pains about the heart accompanying the bloating. Toxic symptoms of dulness, weakness and nervousness were marked. Examination revealed a short, squatty built young woman with normal physical findings with the exception of a low-lying, freely movable cecum, a very spastic, tender colon and a 4+ ileocecal regurgitation. The patient was then placed in hospital under control and an attempt made to overcome the local stasis, but during a period of three weeks this was found to be wholly impossible. The vomiting and looseness of the bowel was much aggravated by the dietetic regimen. Later, at home for five months, the patient tried in vain to obtain relief by following the same principles more slowly. In May, 1921, the abdomen was explored with the belief that an unrecognized gall-bladder disease would be found. This, however, was not the case. The cecum and right colon were long and loosely attached. It could be entirely delivered outside of the abdomen. There were some bands about the colon, which extended to a point above the duodenum, and the appendix was long and free. The appendix and the pericolic bands were removed and the right colon fixed upon the kidney shelf. Recovery was prompt. The tender, spastic colon relaxed under a bland diet and the symptoms of vomiting and diarrhea disappeared rather quickly. The colon was examined by barium enema July 27, 1921, when a 3+ ileocecal regurgitation was still present; all diarrhea, however, had left. February, 22, 1922, the patient reported feeling perfectly well, and on that day a 1+ regurgitation was found.

**Discussion.** We have shown in our clinical work with gastrointestinal patients that the relief of symptoms does not depend upon the removal of an ileocecal regurgitation, and, also that a distinct ileum stasis is sometimes not recognized by ill feelings. We have likewise shown that some of these individuals have not obtained relief under the most careful control until after the loosely fixed right colon has been properly placed upon the kidney shelf, which alone seems to permit a regulation of the bowel that affords relief. The fixation of the colon alone seldom or never permits the bowel to regulate itself. A process of dietetic training, incident to the

tender, spastic colon, is necessary and oftentimes it must be carried out for a period of years. Again, other individuals with mutilated colons, short-circuitings, partial colectomies, colectomies, with a persistently dilated terminal ileum, persistent stasis and free regurgitation, may be made well and free of symptoms by proper control. Why are these things so? What fundamental principles of the gastro-intestinal tract underlie the relief from such varying pathological states? It is evident that if there is a common basis for these conditions it must be found in the motor mechanism of the bowel itself.

For some years the nodal and bundle system of the heart have been quite accurately known; the rhythmicity of the heart beat being directly under the control of these systems. In the 1915 Cavendish Lecture, Arthur Keith described certain more or less ill-defined nodal zones of neuro-muscular tissue in the intestinal tract—a supposed specialization of the myenteric plexus. He found these specialized zones about the cardiac orifice, the duodenum, the jejunal junction, the ileocecal region and in different portions of the colon and rectum. To them he ascribed a pacemaker function similar to those of the nodal system in the heart.

Recent advance in the knowledge of the motor function of the gastro-intestinal tract from the physiological side has become of greater importance and is much more satisfying in its conception of what actually underlies the mechanism of peristalsis. Much of the experimental work, as well as the conception of what these experiments have meant, has been done by Alvarez<sup>13</sup> of the Hooper Foundation of the University of California. To us his work gives an explanation of peristalsis that meets every clinical requirement, with the possible exception of a mechanical part played by a loosely attached cecum.

Gradients of rhythmicity, irritability, and of the latent period of contraction have been demonstrated in the stomach, small intestine, cecum and colon. Using the CO<sub>2</sub> production and the catalase content of the tissues (catalase is the ferment which liberates oxygen from hydrogen peroxide) as indices of metabolic activity, Alvarez has shown that similar gradients of metabolism exist more or less uniformly in a decreasing degree as one goes down the tract, and it is believed that it is this gradient of metabolic activity which gives rise to the gradients of rhythmicity, irritability and latent period that determine the direction of peristalsis.

Referring again to the heart, Hyman<sup>15</sup> has likewise found a gradient of metabolic activity underlying the difference in rhythmicity of the muscle bundle system of His.

Lower gradients of metabolic activity are found in the cecum than those which exist both in the terminal ileum and in the ascending colon immediately above the cecum. Excised muscle strips

from the cecums of rabbits and guinea-pigs show little tendency to contract rhythmically. The irritability is low and the latent periods are long. The catalase content of the tissues is low, indicating a low metabolic activity. There is, however, a gradient of catalase content from the tip of the cecum to the base, indicating a metabolic gradient which determines the direction of contraction waves when they occur. This motor mechanism of the cecum doubtless plays its role in the puddling of its contents, as it has been termed, and also aids in the absorption of its liquids. Is it then not logical to believe that a freely suspended, unattached cecum in man, who habitually assumes an erect posture, may lose enough of that mechanical support given to the firmly fixed cecum lying on the kidney shelf, a plane of about 50 degrees with the horizontal, to interfere with the emptying of its contents very much or even to make it impossible? This is exactly the condition met with clinically in some instances of mobile cecum, both with and without the presence of ileocecal regurgitation. This finding we have proven in a number of cases by demonstrating the irrelievability of the cecal stasis with the patient under rigid control, and then by noting its easy relief after a simple fixation of the cecum and ascending colon on the kidney shelf has been done. Clinically, the following general statements hold true; namely, abnormal cecal stasis is relatively seldom found in a firmly fixed right colon with a high position of the cecum; conversely, cecal stasis is frequently met with in a loosely suspended right colon with mobile cecum. The same statements are true of ileocecal regurgitation and of chronic constipation in general.

Another thing of great importance determined by Alvarez has been the fact that these normal gradients of rhythmicity, irritability, latent period and catalase content are much disturbed and disarranged by general illness, local abdominal lesions and by purgation. Muscle segments from the intestinal tracts of sickly animals, or from those that have been purged freely, beat poorly, irregularly, and become fatigued easily. We have known for years in a clinical way that the overcoming of a general asthenic state was one of the most important factors in overcoming the motor disturbances of the gastro-intestinal canal. In the same manner we have repeatedly shown the harmful effect of all catharsis in the regulation of chronic constipation. It is impossible to overcome an intestinal or colonic stasis and make use of catharsis at the same time, or even of flushings and enemas to any extent. This principle is fundamental. An intestinal stasis which can not be overcome by dietetic methods under rigid control has some form of surgical barrier present in the abdomen which prevents it. It may be a hidden gall-bladder or appendix disease; more rarely is it ulcer or widespread pericolic bands; and still more rarely is it an irrelievable intestinal stasis itself. This principle forms the

basis of what we choose to call our "therapeutic test" of the so-called borderline abdominal case. A patient with chronic abdominal symptoms, in whom no satisfactory explanation for the symptoms can be found by examination, is put through this therapeutic test before operation is advised. Many hidden surgical lesions are found in this way because such lesions will often produce an acute upset under the pressure of a bowel regulation regimen. On the other hand, a much greater percentage of patients with similar symptoms are relieved quickly of distress and the basis of it is shown to be some form of a relievable motor disturbance by its quick response to the same procedure. Ileocecal regurgitation, with and without other local lesions, occasionally, although rarely, enters the field of true surgical indications. It is by this therapeutic test that we have separated the few surgical from the many dietetically controllable cases.

**Conclusions.** 1. Competency of the ileocecal valve in some persons may be demonstrable throughout a period of one hour. It may be assumed to be permanent in them.

2. Ileocecal incompetency occurs without symptoms in a moderate percentage of healthy persons. The majority of the instances occur in conjunction with a mobile cecum. In such persons the degree of regurgitation is usually small.

3. The incompetency is of frequent occurrence in persons who have abdominal distress.

(a) The relief of such symptoms may or may not be accompanied with the overcoming of the regurgitation.

(b) The relief of such symptoms seems to be directly related to the reestablishment of the normal gradient of intestinal forces, as suggested by Alvarez's work.

4. Over 80 per cent of cases of ileocecal incompetency occur in association with a determinable degree of cecum mobility.

5. A small number of ileocecal regurgitation cases, with and without mobile cecum, are found in which neither the stasis nor the symptoms of it can be removed by dietetic measures alone. The end-results following the surgical treatment of such cases justify the surgical measures employed.

6. The operative procedures alone do not relieve the patient of his distress. They merely place the patient back into the large group of relievable cases which depend upon dietetic and reconstructive methods of treatment for their cure.

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## EPIDEMIOLOGY OF ACUTE RESPIRATORY INFECTIONS, AS DEDUCED FROM A MILD EPIDEMIC OCCURRING IN THE 8TH CORPS AREA, MARCH, 1922.

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ABOUT March 1, 1922 a sudden outbreak of acute respiratory diseases occurred among troops stationed near San Antonio, Texas. The brief duration of the epidemic, its rapid development and equally rapid decline, challenged investigation and eventually led to a comparison with other local epidemics occurring in different stations of the 8th Corps Area (shown in Fig. 4).

The persons affected were for the most part not dangerously ill. There were no deaths among 650 cases admitted to Station Hospital, Fort Sam Houston, Texas. Temperatures averaged 102° F. among the different cases, although individuals occasionally showed fever up to 104° F. The symptoms were those usually described in mild or moderately severe catarrhal fever. Onset was usually with generalized aching, headache, prostration, chilly sensations giving way to fever, cough and often some soreness of the throat. Most of the patients felt well after two or three days in the hospital and were able to return to duty within a week or ten days. There was no pneumonia or empyema, except perhaps in one or two instances. Sinusitis occurred only rarely.

In view of the lack of definite diagnostic points for identifying influenza, it was deemed advisable to follow the plan advocated by the Surgeon-General in the following words which he applied to the epidemic of 1918: "The only way to obtain a correct picture of the epidemic during the autumn (1918) is to combine both the admissions and the death rates of pneumonias, of influenza and of the common types of respiratory diseases. The excess then of the combined rates over the ordinary rates for this class of diseases for the same period of the year will probably give approximately the correct figures for influenza with its complications."

The accompanying charts and graphs represent therefore all cases of pneumonia, influenza, and ordinary types of respiratory

diseases occurring within certain organizations and certain stations during the first three months of 1922. Fig. 1 represents the epidemic as it was reflected in the daily admissions to Station Hospital, Fort Sam Houston, Texas. The number of admissions for acute respiratory disease increased rapidly from an average of 1 or 2 cases daily up to 46 cases on March 10. The decline in numbers was almost as rapid, having reached an average of 3 or 4 cases daily by April 1. On Saturdays and Sundays there were fewer admissions, due to the reluctance of soldiers to report sick on holidays. A miniature preliminary epidemic or "flare-up"

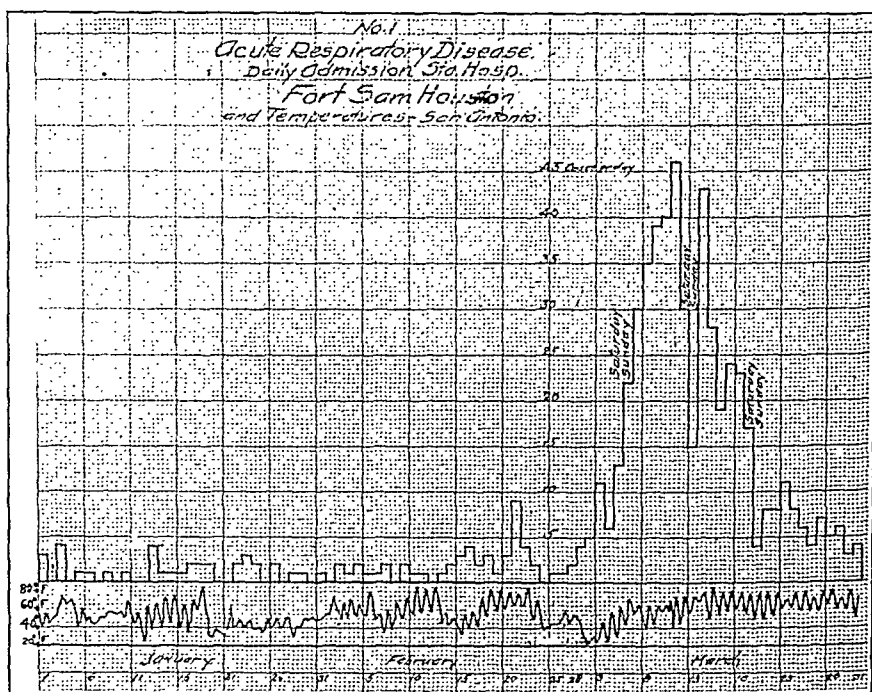


FIG. 1.—Showing number of admissions daily due to acute respiratory disease; Station Hospital, Fort Sam Houston, Texas, first quarter of 1922. Also showing fluctuations of temperature at United States Weather Bureau observation station two miles away.

occurred on February 21. This miniature forerunner of the large epidemic, had it affected only one station or organization, might have been plausibly regarded as the focus from which the larger epidemic developed. As a matter of fact, however, the group of 9 cases came from the following sources: Infantry A, Camp Travis, 2 cases; Infantry D, Camp Travis, 1 case; Camp Stanley, 2 cases; Camp Normoyle, 2 cases; Fort Sam Houston, 1 case; Station Hospital (attendant) 1 case. When analyzed, therefore, this group partakes more of the nature of a group of sporadic cases. During January and February, sporadic cases occurred in a more

or less irregular series from the various organizations, as shown in Figs. 2 and 3. Unquestionably, there was a "flare-up" about February 15 to February 22, especially shown in Fig. 1.

Fig. 3, however, shows all cases that appear in Fig. 1, and also those cases at certain nearby stations that were not sick enough to be transferred to Fort Sam Houston. Fig. 3 therefore, shows that Camp Stanley, twenty-three miles north of Camp Travis, and Camp Normoyle, four miles west of Camp Travis, were affected by a milder and earlier epidemic than Camp Travis. There was abundant passing back and forth between Camp Stanley and Camp Travis. Regiments of engineers, of infantry, and of artillery marched to Camp Bullis adjoining Camp Stanley, camped there for days and marched back to Camp Travis in the period immediately preceding the epidemic. While the larger epidemic affecting Camp Travis and beginning about March 1, could have been based on the preliminary "flare up" at Camp Stanley, nevertheless the organization suffering earliest invasion and highest incidence had not left Camp Travis. Certain environmental conditions, which apparently had a bearing on the high incidence in the organization will be mentioned later.

Fig. 2 shows that practically all organizations in Camp Travis were simultaneously affected by the epidemic. Fig. 4 shows that Fort Sill, Oklahoma, experienced an epidemic of acute respiratory disease just one month earlier than most of the other stations within the 8th Corps Area. While the remaining stations were not affected at precisely the same time, the graphs show that they were affected at approximately the same time. The epidemic at Fort Sill lasted about the usual length of time, *i.e.*, about a month. It is worthy of remark that the great epidemics affecting the cantonments in 1918, also lasted about a month and showed a symmetrical curve as rapidity of spread and rapidity of retrogression were about equal. From Fig. 2 it can be seen that Infantry Regiment A, presented the highest incidence in Camp Travis. Moreover, one battalion was affected exceedingly more than the others; one company of this battalion had a decidedly higher incidence than any other company in the battalion; and in this company the incidence was explosive, about 25 per cent of the personnel of the company having been hospitalized in a single day. Upon inquiry it developed that this regiment had just commenced rifle aiming practice; the battalion affected had simultaneously discarded the service blouse which interfered with the aiming practice. Part of the aiming was done in the prone position on the ground, which was still cold and somewhat damp. The severest cold wave of the season had just swept down over the camp, and as a result of the cold weather the men were lectured indoors for several days immediately preceding the discarding of their blouses and the beginning of rifle aiming. These facts offer



a reasonable explanation for the exceptionally high incidence in this one regiment. The cold wave referred to came just at pay day, and as Camp Travis is several miles from the shopping district of San Antonio, naturally the soldiers exposed themselves considerably, especially at night, riding to and fro in the open jitney,

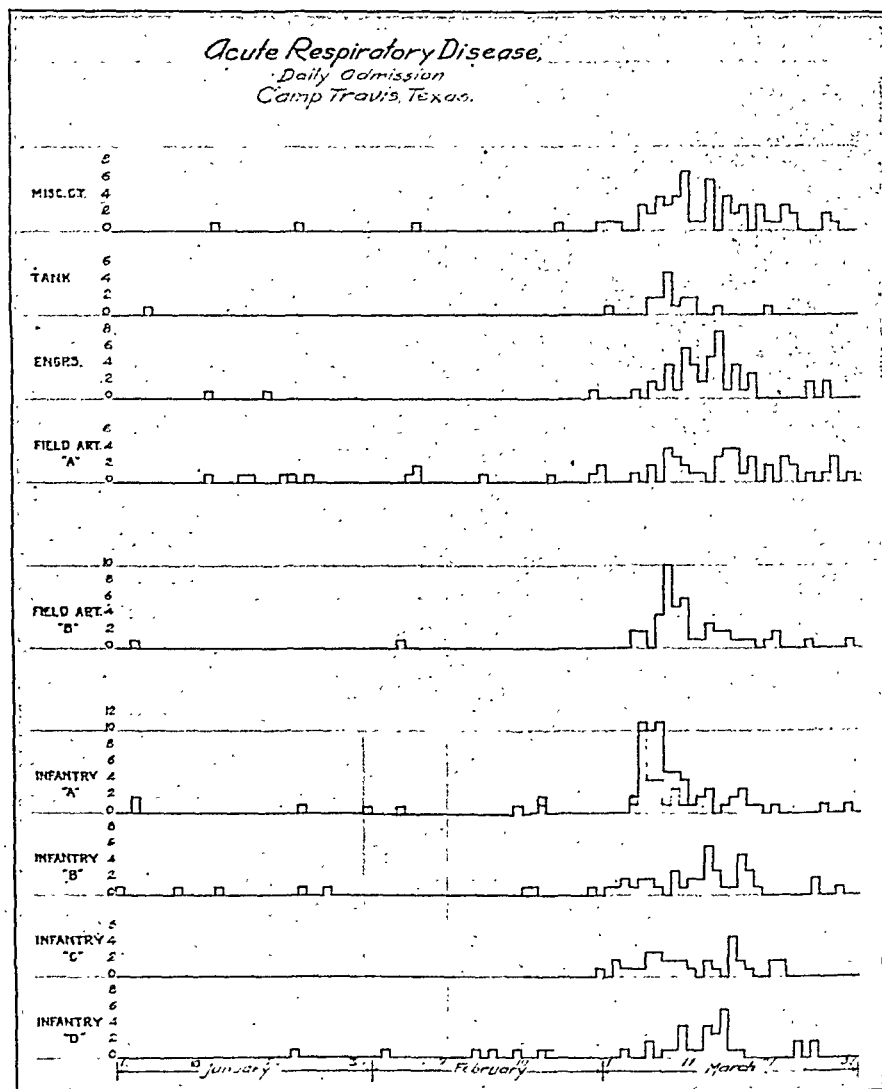


FIG. 2.—Showing daily admissions from acute respiratory disease, first quarter of 1922, among different organizations at Camp Travis, Texas.

which was the main reliance for transportation between camp and city. The severe cold wave, which came at pay day and just when spring training programs were being carried into effect, may have had an influence on all stations within its scope. Fort Sill, Oklahoma, had suffered the severest cold wave of the season imme-

diately preceding the beginning of its epidemic, one month earlier. See Fig. 4 which shows graphs representing the rise and decline of the epidemic at various stations, and which also shows the temperature fluctuations of Lawton, Oklahoma, the nearest weather observation point to Fort Sill. The possible effect of exposure to lowered temperature was investigated so far as 52 soldiers were

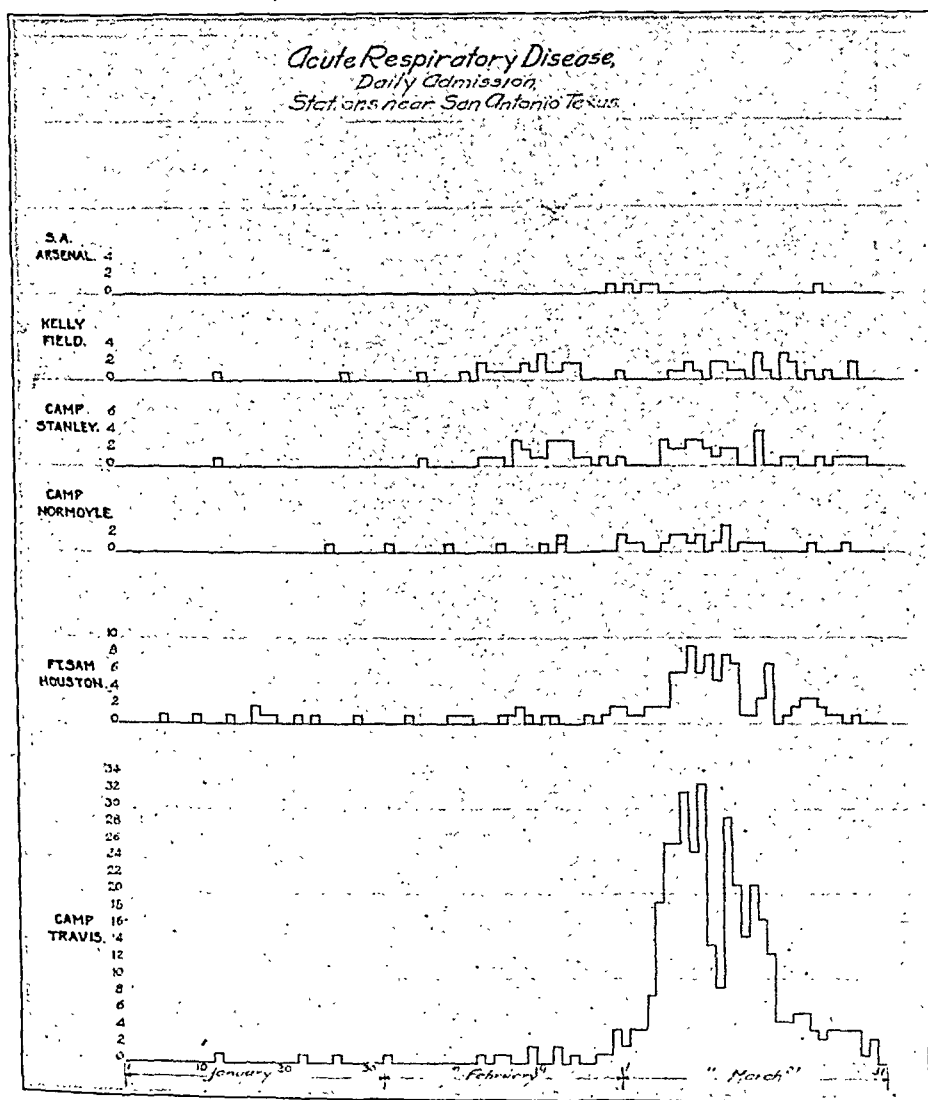


FIG. 3.—Showing daily admissions from acute respiratory disease, first quarter of 1922, at several stations in the immediate vicinity of San Antonio, Texas.

concerned. These men were admitted successively to two wards. Thirty-nine of the 52 gave a history of exposure to lowered temperature.

The name influenza would never have come into being had it not been for the epidemicity which at times characterizes the disease. The individual case of influenza presents no identifying earmarks.

The rapid development and rapid decline of this epidemic correspond to similar traits observed in the epidemics of 1918; hence, this epidemic may be with justice termed influenzal, although the term epidemic bronchitis is more in keeping with our actual knowledge, while at the same time it is more descriptive.

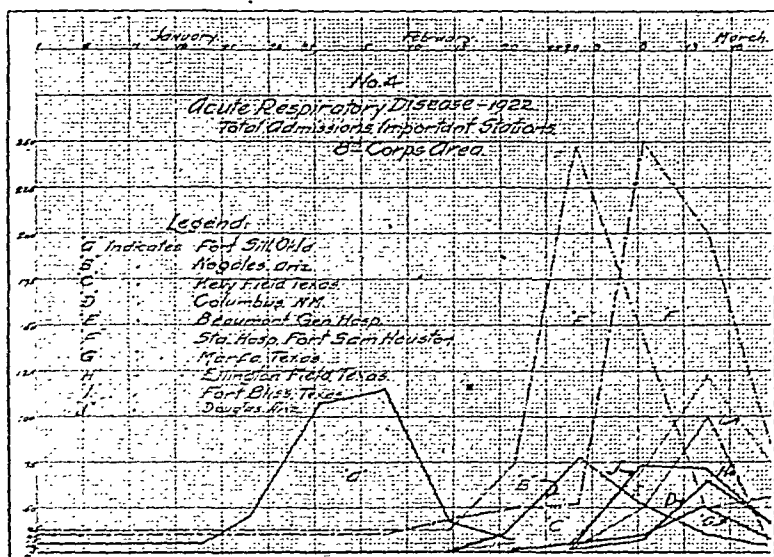


FIG. 4.—Showing weekly admissions from acute respiratory disease at different stations in the Eighth Corps Area, first quarter of 1922.

This influenza epidemic, therefore, bore certain characteristics having a bearing on the etiology of the disease as follows:

1. The epidemic developed in ten days and subsided almost as rapidly.

2. It broke out simultaneously in at least a dozen different places and organizations.

3. It showed a predilection for soldiers who had been exposed to lowered temperature under unfavorable physiological conditions.

If this epidemic was due mainly to transmission of an organism, then the transmissibility of this organism presents certain peculiarities: (a) It is more transmissible than any other infective agent known to man, because under modern conditions of sanitation no other epidemic infectious disease ever affects so many persons; (b) it is more rapidly transmissible than any other infective agent, absolutely defying analysis. Where we would be prepared for an incubation period of twenty-four to forty-eight hours, influenza travels as fast as man can travel and in addition breaks out in myriads of disseminated foci. While trained scientists were in charge of selected persons whose every movement was regulated by central authority and recorded in black and white, the disease has developed where it would and its origin defied detection as

its spread defied limitation; (c) the marvellous transmissibility undergoes rapid extinction with clock-like regularity, regardless of the habits of the people and regardless of sanitary precautions.

The peculiar traits of this epidemic call attention to certain fundamental characteristics of *pneumococci*, the bacillus of influenza, and the other bacterial *flora* which, regardless of any causative influence they may wield, nevertheless are certainly intimately related to the respiratory mucosa. Their continual presence in the air passages is an indication of their adaptation to this habitat, and bespeaks an association between germ and host which must have lasted for ages. During this long period of time, the relations of man and the organism have been marked by an alternation of phase; first, the peaceable or carrier phase; then, the antagonistic or inflammatory phase. No pathogenic strain has ever existed whose being was not, at least to a certain extent, characterized by alternating states; for the pathogenic organism must by definition enter a relatively normal human being and bring about a diseased state. And while it may be granted that the pathogenic organism soon sets up an inflammation in its immediate neighborhood, it must also be recognized that the given organism has resided in relatively normal tissue for a modicum of time. Moreover, many pathogenic organisms are frequently found in healthy individuals, so-called disease carriers, and in these instances the alternation of states on the part of the organism is seen even more clearly, as the organism may live for a time in a healthy carrier, and then may either take up residence in a susceptible person who becomes ill, or may take on virulence toward the carrier himself; and in either event, a setting is furnished for the active or antagonistic phase of the germ's life history.

These manifestations of activity on the part of the germ are naturally of an adaptive nature; being a living creature, its life depends upon its adjustment to its environment, and it is not to be supposed that the variations in the behavior of the organism are a matter aside from its struggle for existence. On the other hand its life history is a record of its past successful adjustment to its environment. And so the alternating phases in the life of the organism are to be looked on as fluctuations of activity in obedience to stimuli from without. Indeed, the asexual division and growth which necessarily characterize the antagonistic phase could not take place unless pabulum were at hand and the environment otherwise suitable.

It is not easy to ascertain just what substances or conditions act as a stimulant to the bacterium to bring on its antagonistic phase, but in general, it is quite clear that the inflammatory state is favorable to the pathogenicity of bacteria. When the respiratory tract is inflamed by measles, the pneumococcus or streptococcus oftentimes becomes awakened to pathogenicity. When the lungs of

the dog are subject to trauma incident to the forcible injection of pneumococcus culture, the culture will provoke lobar pneumonia. In the absence of even slight violence the pneumococci do not show definite pathogenicity toward the lung of the dog. Traumatic pneumonia is a true pneumococcus infection, but the change from quiescence to activity on the part of the pneumococcus is provoked by the inflammatory exudate resulting from the trauma.

Chilling the body surface causes alteration in blood distribution to such an extent that myriads of delicate capillaries within the lung substance are ruptured and some tissue juices and inflammatory exudate are poured out. As a result of the total disturbance in the lung, pneumococci tend to take on virulence, leading to the well known pneumococcus pneumonia following exposure to lowered temperature. Virulence is only manifested in the presence of inflammatory exudate. The invasion of successive lobules of the lung by a pneumonic process takes place from an inflamed locus which serves as a base of operations. Pneumococci often have power to make headway in the lung, once an index of inflammatory exudate is established, whereas they lack the power to inaugurate the first inflammation. As a proof of this, it may be said that the mere introduction of pneumococci into the lung in small amounts simulating natural conditions has usually failed to provoke a pneumonia in experimental animals, but on the other hand it has been possible to provoke a pneumonia in animals by slight trauma plus the pneumococci. During general inhalation anesthesia the mucosa of the respiratory tract is injured and flakes of its epithelium often desquamate off. Some inflammation is associated with the process and the tissue juices and inflammatory exudate tend to provoke quiescent pneumococci present into activity. Mouse peritoneum is very susceptible to pneumococci, and reacts promptly by peritonitis whenever pneumococci are introduced into the peritoneal cavity. That the pneumococcus is stimulated by residence in and on inflamed mouse peritoneum is well known; in fact, it overgrows all other organisms in this habitat. Furthermore, pneumococci grown on mouse peritoneum are more virulent, but this virulence disappears after a few subcultures on artificial media.

Adami says in effect (page 327) "One bacterium cannot cause disease in the normal mammal: when the vitality is lowered it requires several bacteria in close proximity to produce so much discharge that the anti-bacterial substances of the enclosing or surrounding cells become neutralized." I should like to interpret the facts thus:

When the group of bacteria is large enough and virulent enough to provoke an outpouring of inflammatory exudate or lymph, then this latter so stimulates the bacteria that they commence the active or antagonistic phase. Adami says on page 325, "To produce disease we must have a special concatenation of circumstances:

(a) The presence of an excessive number of organisms at one surface region; (b) congestion of a mucous surface with the passage out of an increased number of leukocytes; (c) reëtrance of these at one region bearing the bacteria; (d) habitual or recurrent deposits at one spot so as to exhaust the bactericidal powers of the cells; (e) temporary or habitual lowered vitality of the cells." There is nothing mentioned in this that is inconsistent with the view that inflammatory exudate exerts the decisive influence toward virulence. On the contrary, the first two considerations uphold the view that inflammatory exudate is the important factor, and even almost seems to shadow forth the same thought.

Bails work on "aggressins" goes further. He produced inflammatory exudate from a pleural cavity by injecting typhoid bacilli. The germ-free inflammatory exudate injected with a sublethal dose of the homologous organism produced an acute lethal result. Bacteria which normally could be destroyed within the tissues survived and multiplied when aggressins were injected with them. The aggressins were produced in greater amounts in severe acute strife between the bacteria and the body cells. Only a little was produced in the test tube. It seems plain here that the contribution of the tissues, particularly the inflamed tissues, to the virulence of the organism is the important factor, granted that the aggressins are produced by the tissues plus the organism, reacting on each other. The organism on artificial media, in the absence of strife, produce almost no aggressins. When mutually inflamed, the two produce aggressins in proportion to the acuteness of the inflammation. This affords rather strong evidence in support of the view that inflammatory tissue juices constitute the aggressins. The idea that the bacteria contribute to the formation of aggressins only when in the antagonistic phase is thoroughly in accord with this view, for the bacteria are protoplasmic and in many respects analogous to cells and it appears reasonable to believe that when excessively stimulated both bacteria and tissue cells throw off particles of an irritating or stimulating nature.

Insofar as the aggressins manifest specificity, stimulating only the homologous organisms, Bails' work does not support the view that inflammatory exudate exerts a stimulating effect on bacteria. Nevertheless the numerous additional instances quoted above show that whenever bacteria are in contact with inflammatory exudate they tend to take on virulence, and hence the view is well supported in spite of any specificity which may have been reported in isolated instances.

The view adduced above to the effect that pneumococci and other bacteria are stimulated by inflammatory exudate so that they acquire virulence and enter their antagonistic phase implies that bacteria are subject to fatigue. No responsive physiological structure (unless it be nerve fiber) can functionate continuously.

A bacterium just removed from the highly stimulating inflammatory exudate characteristic of lobar pneumonia would be expected to undergo a reaction and readily lapse into quiescence. This corresponds with the facts; for while not unknown, it is exceptional to have secondary cases of pneumonia following a virulent case. On the other hand, pneumonia carriers abound around the sick room. It appears to be the rule that bacteria having just passed through a stormy period of residence in an acutely inflamed individual tend to take on their quiescent phase, both in the original host, who thereupon has the crisis and enters convalescence, and in contacts, who thus become carriers. It should be noted that the pneumococcus removed from an active pneumonic lesion and deposited on the mucosa of a normal individual undergoes an abrupt change, an abrupt withdrawal of stimulation. The more severe the case, the wider the gap which the organism must span when taking up life in its new abode. Intense virulence then imposes an additional burden on the capacity of an organism to adapt to quieter surroundings, and hence tends to inhibit immediate transmissibility of the disease.

Transmissibility of the organism is inhibited to a less extent, possibly not at all. If there had ever been an experiment performed which consisted in the repeated transfer of virulent organisms in the antagonistic phase from one acutely inflamed organ (in one animal) to another acutely inflamed organ (in another animal) in series, then according to the view hereinbefore set forth the virulence of the strain should have disappeared. The contrary would be strong evidence against the view. I have learned of no such experiment. Experiments in which the organism to be tested is transferred to a normal animal would not be expected to cause early decrease in virulence, because the natural requirements of the strain are satisfied by the alternating states. It should be noted that the antagonistic phase of a bacterial strain must be assumed to outlast several generations. The peculiar fact that fission occurs without apparently modifying the temporary state of the individual as regards quiescence or activity must be explained on the grounds that asexual division is a less complicated process than mitosis, or it must be left to be explained by further study and experiment. In this connection the observation announced by Flexner<sup>10</sup> is of interest. He observed that poliomyelitis virus (maintained by serial inoculation in monkeys) fluctuated, growing progressively more virulent for several months or years and then becoming less virulent for a similar period. Cecil and Blake have expressed the belief that pneumococcus and streptococcus hemolyticus are powerless to inaugurate a primary inflammation when sprayed into the nasopharynx, but that these organisms readily take hold when *B. influenzae* have prepared the way and they have well supported their belief with experiments.

The implantation of a secondary invader of severe virulence on a mucosa already inflamed by a primary organism could well be termed "pyramiding of virulence". That is to say, the contrast between acutely inflamed mucosa and normal mucosa might be so sharp that the virulent organism could not step down successfully without passing into the quiescent phase. But when the virulent organism was transferred from a pneumonic lung, for instance, to a trachea or bronchus already moderately inflamed by *B. influenza*, it might conceivably survive the change without suffering a reaction amounting to quiescence, and might commence the antagonistic phase anew. The longer the antagonistic phase lasts, the greater the tendency to lapse into quiescence. According to this conception, pyramiding of virulence ought to be common during a widespread epidemic such as the influenza and pneumonia epidemic of 1918, but there is no apparent reason why pyramiding should not occur among different strains of any given species.

In addition, since the tissue cells react in one stereotyped fashion to all forms of irritant, it appears reasonable to believe that pneumococci would be as readily stimulated into the antagonistic phase by inflammatory exudate resulting from heat, cold, trauma, or chemical irritant, as by that resulting from *B. influenza*. Hence, the experiments quoted by Cecil and Blake appear to have proved that: "A strain of pneumococci derived from a severe case does not readily continue its antagonistic phase when introduced into normal mucosa of another host, but can be induced to continue its antagonistic phase when implanted upon a mucosa already moderately inflamed by *B. influenza*."

In conclusion a word should be said concerning the relation which the interpretation described in the preceding paragraphs bears toward humoral immunity and lowered resistance. Humoral immunity based on antibodies is usually developed during the antagonistic phase of a pathogenic organism's parasitism and it is believed to be based on a special variety of inflammatory exudate. Apparently the body develops no humoral immunity until such time as it is invaded or attacked by an organism and its products. Of course it does not always do so even then. Hence antibody immunity is not necessarily the most important part of immunity but is simply one special adaptation of the body to ward off germ enemies after they attack. Lowered resistance is a much more vague term but the very essence of the term implies "attack from without." Lowered resistance while really only a paraphrase can be assumed to explain all lack of immunity in the face of attack, but to assume any degree of resistance in the absence of attack is gratuitous as well as without foundation.

The present paper deals with certain factors underlying initiation and cessation of attack and hence the field of discussion is not exactly the same as that involved in humoral immunity and lowered



resistance, the question first to be answered is "Does the given strain of organisms attack the body under the given circumstances?" If this is answered in the affirmative then the resistance of the body consisting of humoral immunity and other factors, comes into play. Furthermore if an attack be granted to have occurred, then the subsidence of symptoms should not be attributed to antibodies or heightened resistance without also taking into consideration the possibility of withdrawal of the enemy on account of exhaustion or similar inherent cause.

It is well known that the crisis in pneumonia cannot be satisfactorily correlated with the antibody or bacterial content of the blood, with the pathology of the lung, or with any other changes in the patient himself. An attempt has been made above to bring the critical phenomenon in pneumonia (*i. e.*, the crisis) into line with the past history of the pneumococcus, with the carrier state, and with the epidemiology of milder respiratory infections in an attempt to deduce an underlying principle, as stated.

**Summary.** 1. This epidemic developed in ten days and subsided almost as rapidly.

2. It broke out simultaneously in at least a dozen different places and organizations.

3. It shows a predilection for soldiers who had been exposed to lowered temperature under unfavorable physiological conditions.

**Conclusions.** 1. The quiescent phase and antagonistic phase tend to alternate with each other in the life history of facultative pathogenic bacteria.

2. The antagonistic phase occurs in response to stimulation applied to the bacterial organism.

3. Inflammatory exudate furnishes the required stimulation.

4. As regards the disease itself, transmissibility tends to be inversely proportional to virulence.

5. No evidence is seen against the occurrence of pyramiding of virulence within a given species of organism.

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## THE USE OF GENTIAN VIOLET IN THE TREATMENT OF EMPYEMA.\*

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My experience within the last year with the treatment of empyema by the aspiration of the seropurulent or purulent exudate, and the introduction into the chest cavity of an aqueous solution of gentian violet has been so satisfactory as compared to the older methods of surgical treatment, especially in those cases in which the exudate is not frankly purulent but a thin seropurulent exudate that I recommend this method of treatment, especially in the early cases.

Empyema is one of the oldest of diseases known. It was known even at the time of Hippocrates and very little progress was made until the last few years in the treatment of this condition. For many years the only facts worth knowing about empyema was that it followed pneumonia; and that its treatment consisted in incision and drainage. The pathology and diagnosis were simple. The operation was simple and for several years empyema seemed to offer no opportunity for more intensive investigation. Now and then an article appeared on empyema, but these concerned themselves merely with surgical technic. In 1914, Wilensky<sup>1</sup> investigated the mortality of empyema at Mt. Sinai Hospital for the preceding ten years; that is, the review that was made was the result of surgical treatment of empyema for ten years, from 1904 to 1914, in empyema resulting before the epidemics of influenza and bronchopneumonia in New York, and showed that even in a good hospital the mortality reached the appalling figures of 28 per cent. And unless one is familiar with the mortality of empyema one is more or less appalled by the statistics of any large hospital in which is treated a considerable number of pneumonias with the resulting empyema. The statistics from the different army camps are also quite a lesson in this respect. And when one has seen the result of operative treatment as soon as the fluid was diagnosed, or by waiting later until adhesions had formed, so as to lessen the amount of lung collapse, one is immediately impressed by the difference in the mortality rate.

Before taking up the use of the aniline dyes in the treatment of this condition it is very necessary that the pathology and pathogenesis of the common empyema is understood. Moschcowitz<sup>2</sup> in his extensive work has shown that there are three stages in the development of empyema.

### I. The formative stage.

\* Read before the Jackson County Medical Society, Kansas City, Mo., November 28, 1922.

## II. The acute stage.

## III. The chronic stage.

And in any empyema in which frank pus is obtained it is in this third stage. It is an end product or the terminal even of an infective process in which the first stage is a pneumonia with a small serous pleurisy, and the second is a pneumonia with a greater exudate of seropurulent material; and the third stage is frank pus. In a great number of pneumonias, especially if there is any pleural involvement, there is also a pleural effusion of greater or less amount. I feel perfectly sure that a considerable number of these are overlooked, which is not necessarily a serious thing, because so small an amount of fluid does no harm; in fact, in the pleuresies with acute pain it is a relief to the patient as soon as sufficient fluid forms. This serous fluid becomes infected by an abscess which lies adjacent to the pleura, covering the lung, over the affected area. These abscesses rupture into the pleural cavity, thereby infecting the fluid which is in the pleural cavity. This fluid, when infected, becomes seropurulent and at a later stage purulent. This purulent exudate is later encapsulated due to a fibrinous deposit around the periphery which may be either single or multiple encapsulations. It is very important that we remember the fact in reference to the surgical treatment which is, that a serous and seropurulent fluid is always free while a purulent fluid is encapsulated. In other words, a working rule is, that when the fluid settles out into two layers upon standing, an open drainage should not be done because of there being no, or few, pleural adhesions and the resulting collapse of a large part of the lung. And usually in this stage there is still present a pneumonia. If the purulent exudate has not settled out into two layers the patient has usually recovered from his primary pneumonia, adhesions have formed, encapsulation has taken place and drainage can be accomplished without the resulting lung collapse.

It makes a difference in the mortality varying from 20 to 60 per cent if the patient is operated in the encapsulated or acute stage of the disease. The proper treatment for the acute stage of the disease is aspiration by some closed method insuring that no air gets into the pleural cavity. Every case differs as to the amount of fluid formed and at the rate of formation. We have all seen these cases, especially of streptococcic pneumonia that within a few hours one side of the pleural cavity is half filled with a seropurulent exudate. Others fill very gradually. Autopsy results show that many cases go unrecognized. It was in the first two stages; that is, the formative stage or the acute stage in which pneumonia is still present that Major<sup>3</sup> devised the use of gentian violet treatment.

Before taking up the treatment proper and the indications let me review briefly the use of dyes in medicine. It has been known

for a long time that certain dyestuffs have a selective action on certain bacteria or classes of bacteria. Among the early workers were Rozsahegyi,<sup>4</sup> Shillings,<sup>5</sup> and Koch<sup>6</sup> who showed that various organisms, among them the tubercle bacillus are inhibited in their growth, bacteriostasis, or killed by dilution of dyes. This susceptibility of bacteria to various dilutions of different dyes was pointed out by Rozsahegyi<sup>4</sup> and practical application was made by Drigalski and Conradi<sup>7</sup> in the isolation of the typhoid bacillus. Bacteria were found to vary in their susceptibilities to any particular dyestuff and dyestuffs to vary enormously when used against the different groups of bacteria.

Much work has been done to correlate the chemical structure of dyestuffs and their selective action upon the group relationship in accordance with their dye susceptibilities.

The work of Churchman<sup>8 9 10</sup> who showed the definite relationship between the Gram stain and the susceptibility to dye action, was the later attempt along this line of investigation. In his later work he has pointed out that Gram-positive organisms are more susceptible than Gram-negative bacteria, not only to stains of the pararosalin series, which are used in the staining methods, but also to other groups of dyestuffs as well.

Churchman<sup>11 12 13</sup> used gentian violet successfully in closed cavities in joint infections. He has since shown that besides the Gram-positive organism being susceptible to gentian violet, that the Gram-negative organisms are susceptible to acid fuchsin.<sup>14</sup> Beside the above work; Gay and Morrison<sup>15</sup> working on rabbits produced experimental streptococcus empyema and used a great number of dyes in the treatment of this condition. However, their results were not very satisfactory and their method of application is not the same as used by Major<sup>3</sup> or myself. Other work that has been done is by Waters<sup>16</sup> of the Loomis Sanitarium who reports 2 cases of empyema following artificial pneumothorax for tuberculosis which developed a secondary infection in the plural cavity. One of his patients, especially, shows a very nice response to this treatment. The patient was in a critical condition and the pleural cavity was washed with first a saline injection and later with 1:5000 gentian violet and after several minutes the fluid withdrawn. Later 150 cc was left in with remarkable results. The temperature dropped from 105° F. to below normal and the pulse from 160 to 90 and remained there. The treatment was continued the following day, then every other day until the secondary infection was under control. The other case reported by Waters,<sup>16</sup> is that in which there was removed from the pleural cavity 750 cc of thick gray pus showing staphylococci and a few Gram-positive diplococci. After treatment the temperature curve fell below normal within forty-eight hours. Waters<sup>16</sup> ascribes his results to first, the mechanical removal of infected exudate

from the chest and thorough cleansing of the pleural surface; second, the application of an efficient chemical agent by direct and effective contact with this surface. The action of the dyes on pyogenic organism *in vivo* Churchman<sup>8 9 10</sup> characterizes bacteriostatic rather than as bactericidal and his experiment indicates that it has considerable power of penetration and that its effects are manifest in comparatively weak solution.

The experience following the two hasty operative intervention in empyema was so uniformly noted in the influenza epidemic as to constitute a most important single observation made on this subject during the past five years. Rodman<sup>17</sup> noted in his work that the mortality was 45 per cent in the cases in which the method of early operation was employed. Stone<sup>18</sup> reported the mortality of 61.2 per cent. Following a series of such experiences reported from various parts of the country the method of preliminary aspiration rapidly became the method of choice and its value was emphasized particularly in the report of the Empyema Commission<sup>19</sup> and in a more recent article by Moschcowitz.<sup>2</sup> A number of methods of closed drainage also were used. The method of Mazingo<sup>20</sup> irrigating through a catheter; the method of Harloe<sup>21</sup> who inserted a catheter into the chest through which pus was aspirated at various times and which was clamped off during intervals. It was due to the early results of aspiration before the operation that Major<sup>3</sup> conceived the idea of using some sterilizing agent in the pleural cavity.

We have followed rather closely the original technic described by Major.<sup>3</sup> Our technic is as follows: All cases in which a sero-purulent exudate in which there are organisms are treated. In all of our cases with seropurulent exudate organisms were found. The chest over the fluid area is anesthetized with 0.5 of 1 per cent novocaine. The aspiration is done with a 50-cc Luer syringe connected to the needle by a piece of rubber tubing two to three inches in length fitted with adaptors to fit syringe and needle. This prevents air entering the chest at the time of disconnecting syringe and needle and also is not likely to injure the visceral pleura and the lung by movements of the patient or by connecting and disconnecting the syringe. A nurse or assistant maintains the position of the needle. The fluid is aspirated until the cavity is almost dry, this to be determined by the patient beginning to cough. One precaution we have observed is that during the first aspiration if there is a large amount of fluid, that we did not take out an unnecessarily large amount, although we have never seen any bad results from slow aspiration. Then one-half as much aqueous solution of gentian violet (1:2500) as fluid removed is slowly injected into the cavity. The fluid is first warmed to body temperature. By a later work of Churchman<sup>22</sup> we know that if the fluid is warmed above body temperature it has more of a bactericidal

value. This fluid is allowed to remain until the next aspiration which should be done from one to five days, depending upon each individual case. During the second and following aspiration a solution of 1:1000 is used. In all there were treated 18 cases of empyema. In none of these was a rib resection done, all clearing up with the use of gentian violet with the technic as described above.

In 4 of our cases at the first aspiration was obtained frank pus. In 2 cases the fluid was serous but organisms were isolated from the fluid at the first examination, the remaining were the typical seropurulent fluid. In 3 cases a chlorazene solution 0.5 of 1 per cent was injected to dissolve the exudate which had coagulated and could not be aspirated through the aspirating needle until dissolved. Two of these cases were seen late in the course of the disease. The first was a girl, aged seventeen years, who entered St. Luke's Hospital with a history of having had pneumonia three weeks previous and being told by her attending doctor she was well. She came in complaining of fever and sweats and a physical examination showed fluid in the right pleural cavity. On aspiration only 300 cc of fluid were obtained with great difficulty, the syringe stopping up numerous times during the aspiration. The mother of the girl refused surgical interference and 50 cc of 0.25 of 1 per cent chlorazene was injected. The following day 600 cc of fluid was obtained and 250 cc chlorazene 0.5 of 1 per cent was injected. Then large amounts of fluid was obtained and the gentian violet treatment carried out, with occasionally using just enough chlorazene solution to keep the fluid thin, 50 cc every other aspiration being about the amount used. In 2 cases a very small catheter was inserted between the ribs by Dr. Elmer Twyman, one because we felt there was fluid that we were not obtaining and the roentgen ray showing a shadow of which we were in doubt, and the patient being seriously sick we decided to try to obtain more pus. The catheter was inserted through a trocar and kept air-tight, irrigation being done through it. The patient had a pyemia manifest by multiple abscesses throughout his extremities and by double acute suppurative otitis media and at a later date double mastoiditis and was operated upon by Dr. O. J. Dixon. As soon as the multiple foci cleared up the chest improved. We do not feel that we gained much, if anything, by the catheter over the ordinary gentian violet method. The infection was Type III pneumococcus from which there is a high mortality and the exudate never reached the thick purulent stage. This patient was in the hospital the longest of the series, being in the hospital one hundred and forty days, and during that time having first a left lower lobar pneumonia, later a pneumonia of the entire right lung, then the empyema, multiple abscesses and double mastoiditis. The second case in which a catheter was inserted by Dr. Twyman was one in

a young boy whom it was almost impossible to treat by aspiration on account of the pain of aspiration. He was also seen late in the purulent stage and chlorazene and gentian violet were used as above.

In 1 case that had a streptococci pneumonia first on the left side, then on the right, developed a lung abscess on the left and an empyema on the right. In this case he was expectorating quantities of a very foul smelling material and drainage being somewhat worse upon lying on the right side. Physical examination showed dulness at the right base due to fluid and at the inferior angle of the left scapula there was an area of dulness. This was explored with a needle and lung tissue was encountered. Going a bit deeper was obtained 300 cc of foul purulent material that the patient had been expectorating. When the cavity was aspirated the patient said he could feel air being drawn in through his nostrils. The 100 cc of a 1:1000 gentian violet solution was instilled and part was immediately coughed up by patient, the remainder during the next few hours. After two aspirations and instillations the lung abscess ceased draining. The empyema of the opposite side was treated in the usual way and no fluid was obtained after the fifth aspiration. The other cases were the usual cases of seropurulent empyema and all responded. There was 1 patient that has only 1 aspiration and instillation. One had 2 and the others varied from 4 to 14. The patient with the 14 aspirations did not improve after 10 aspirations. About every four days the exudate would reaccumulate and about the same amount would be aspirated. The patient I had previously treated for lues, two years before; he was put on mercury and immediate improvement followed.

The different type of organism seem to have but little to do with the recovery of the patient by this method. The Type I pneumococcus becomes a thick purulent exudate very early, while Type III and streptococcus are seropurulent for some time.

I have also confirmed the observation of Major<sup>3</sup> that, in some of these cases of empyema, soon after the injection of gentian violet some is expectorated by the patient, and in some of these cases two or three days later they may suddenly expectorate some of the dye. This probably explains why some patients choke and cough so readily with the use of Dakin's solution in the pleural cavity, the Dakin's solution being very irritating to the bronchi. In 3 of the cases multiple pockets were found. One feels that such is the case when after an aspiration the temperature fails to fall almost, or down to normal. One should not delay the aspirations until the patient starts to have the profuse sweats. It is realized that this method cannot be universally, successful so one must keep his patient under constant close observation, and must do repeated physical examinations, and know when to aspirate the chest.

It is impossible to predict, after an aspiration, as to what the temperature will do. It always falls, but to a variable degree, depending somewhat upon the resistance of the patient to the infection and upon the amount of the seropurulent exudate aspirated. This seropurulent exudate in some cases is very toxic and after aspirating large amounts, and in some cases a small amount, the temperature will fall almost, if not to normal. The injection of the dye seems to have no immediate effect other than replacing the toxic exudate. I have replaced rather large quantities with the dye and have never yet seen any bad results. There seems to be a very low toxicity of the dye. In this respect gentian violet has an important advantage over most antiseptics and chemical agents in its low toxicity and the absence of symptoms of pleural irritation following applications. Considerable amount of solution can be left in the pleural cavity.

Furthermore, these cases should be recognized during the acute stage while the fluid is seropurulent, as treatment at this stage is much easier because the exudate has not undergone organization and encapsulation. The advantage of this method consists in that a great number of patients with empyemas are treated early in the disease while they still have pneumonias, that they are cured by the time the results of the pneumonia are over, that if one is treating them by the aspiration and instillation of gentian violet during the acute stage they certainly are not going to kill the patient by recommending or doing an open drainage with the resulting lung collapse and death which usually takes place in this acute stage; that the gentian violet is a perfectly safe, as well as sane treatment in that it has a great bactericidal value, that there are no reactions either locally or generally and that the patient improves following the treatment, as is evidenced by our report of 18 cases, none of which had a rib resection. And in the 2 in which a closed thoracotomy was done very little improvement of the syringe method was noted. A large majority of these patients are out of the hospital much sooner than they would be if we had to wait until the pus became a thick pus before doing a rib resection. There are some, as is evidenced by our 1 case, with whom length of time in the hospital is not materially shortened. In some of our cases only 1 or 2 and not more than 4 or 5 aspirations were necessary. The average length of time in the hospital is much shorter than the older methods. The resulting deformity that occurs, especially in young adults, is materially lessened.

**Summary.** Eighteen cases of empyema are reported treated by the use of aspiration and injection of an aqueous solution of gentian violet one-half as much solution being injected as fluid removed, fifteen cases being treated while the disease was in the seropurulent and early purulent stage and 3 in the encapsulated stage. In the 3 cases which had organization of the exudate



0.25 to 0.5 of 1 per cent chlorazene in small amounts were injected to dissolve the exudate. Novocaine 0.5 of 1 per cent was used locally to anesthetize the skin and peripheral pleura. This method can be used successfully both on the early and late cases, but is especially advised on the acute cases of empyema before encapsulation and while pneumonia is still present.

**Conclusion.** In conclusion I would recommend the use of gentian violet in the treatment of all acute empyemas, or in all empyemas in which the fluid is seropurulent, which indicates adhesions are not formed and encapsulation has not taken place and pneumonia is still present. The surgical mortality in these cases is especially high. By this method a certain number will clear up without further treatment. If they do not clear up no time is lost and the patient is in a better condition for surgical drainage when the proper time comes.

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## REVIEWS.

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THE PRINCIPLES AND PRACTICE OF PERIMETRY. By LUTHER C. PETER, M.D., F.A.C.S., Professor of Ophthalmology in Temple University and in the Graduate School of the University of Pennsylvania, etc. Second edition. Pp. 281; 161 illustrations, including 5 colored plates. Philadelphia: Lea & Febiger, 1923.

THE author has in great part rewritten the former edition, giving particular attention to the sections on methods, technic, instruments and charts.

The subject of perimetry is not a new one and constitutes a chapter in text-books on ophthalmology. Fuchs, de Schweinitz, Weeks and others have not neglected this subject in any particular.

This volume contains a bibliography of about fourteen pages, which confirms the fact that many have contributed to this subject and the author must have spent much time compiling the matter to date. Such a book is, therefore, a ready reference in the library of any active ophthalmologist.

Drs. Ferree and Rand have certainly earned an international reputation and are entitled to the thanks of each oculist for their contribution to this subject. It is hoped that eventually their perfected perimeter will be placed on the market.

Speaking of the use of the blackboard and campimeter, Wilbrand states: "This method suffers from the fault that the various parts of the retina are measured from different distances. The greater the distance from the eye, the smaller the retinal image must be, and the less bright the examined object becomes. Therefore, as the same object is used for examining the various parts of the field of vision, different standards of light and size should be used."

Von Graefe first introduced the use of the blackboard for mapping out the fields of vision, and afterward this was much improved by de Wecker. It is now almost entirely discarded for the arc perimeter.

Very few oculists of experience will agree with the author who states on page 93: "It is utterly impossible to make a satisfactory study of the blind spot of Marriott on the perimeter." There are a few corrections which the author should take into considera-

tion when a future edition is called for. In describing Plate IV on page 60, "A" and "B" do not appear in the illustration. There is also a mistake when the author states that the left side of the blue chart is a darker shade of blue than the right half; he certainly means the reverse. The word "perimetric" appears conspicuously throughout the volume, very properly so, and it seems a great pity that in such a neat volume the author is not more meticulous, as he speaks of "physiological," "pathological," "microscopical," "anatomical," so frequently using the final "al," which should be omitted.

It is a pleasure to quote the author when he states that "Perimetry is but the handmaiden of ophthalmology, in itself it is incomplete, but when associated with certain other facts it becomes indispensable." T.

CLINICAL TUBERCULOSIS. By FRANCIS MARION POTTENGER, M.D.  
Second edition. Two volumes. Pp. 707 and 725. St. Louis:  
C. V. Mosby Company, 1922.

IN this work the subject of pulmonary tuberculosis is fully considered from various angles. Some of the chapters are highly speculative and theoretical, but in these there is always a practical application apparent. Chapters on pathological changes in tuberculosis, the sources and routes of infection and the factors which predispose to tuberculosis, are clearly and concisely written and give briefly a clear *resume* of accepted beliefs and observations on these points up to the present time.

A long chapter on the nervous system in tuberculosis and the vegetative nervous system in this relation to diseases of the lungs is more novel in its treatment. The author has written widely on this subject in the past and where it is approached in this book his writing is particularly fluent. Some of this matter will doubtless stand the test of time. Some of it, of course, will not. How much is solid cannot at present be known, but there is food for much thought in these chapters.

Close attention is paid to physical examination of patient and particular stress is laid on the noting of changes in structure and tissues outside the chest. Muscle hypertonus and atrophy, trophic changes in the skin and subcutaneous tissues and alteration in chest movement are discussed fully. In the many case histories and clinical records inserted or appended, it will be noted that all these points are routinely observed and recorded in an exceptionally thorough manner.

The chapters on the diagnosis of early tuberculosis are excellent. There is an interesting discussion on the roentgen-ray as an aid to diagnosis and the interpretation of roentgen-ray plates. The

chapter on laboratory methods by J. E. Pottenger gives some useful points regarding the standardization of examinations of sputa. The chapter on "Influenza and Tuberculosis" is well presented, but might have been treated more fully in so exhaustive a volume published just after the influenza epidemic.

Throughout this work a constant endeavor to explain the physiological factors concerned in producing signs and symptoms makes the book interesting and Dr. Pottenger's really authoritative work on physical diagnosis marks the book as one of value.

T.

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BRONCHOSCOPY AND ESOPHAGOSCOPY. By CHEVALIER JACKSON, M.D., F.A.C.S., Professor of Laryngology, Jefferson Medical College; Professor of Bronchoscopy and Esophagoscopy, Graduate School of Medicine, University of Pennsylvania. Pp. 346; 114 illustrations and 4 color plates. Philadelphia: W. B. Saunders Company, 1922.

THIS small volume is based on the author's larger and earlier book, *Peroral Endoscopy and Laryngeal Surgery*. A full description of the endoscopic instruments employed in the author's clinic is given and their particular uses considered in detail. The anatomy of the larynx, trachea, bronchi and esophagus are discussed from the standpoint of the endoscopist. The various endoscopic operations are described with remarkable clearness and particular attention is paid to the difficulties encountered in each and the discussion of methods of avoiding or overcoming these difficulties shows the author's wide experience, clear thinking and ingenuity.

To the physician or surgeon wishing to employ endoscopy, Dr. Jackson's authoritative and exhaustive works are, of course, indispensable, but there is much of interest and value for the general surgeon, the laryngologist and the internist to be found in this book. The observations on esophageal diverticulæ are valuable and his work on foreign bodies in the air passages is classic. His descriptions of the physical findings in this condition are probably the best publications on this subject.

T.

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INTERNATIONAL CLINICS. Volume II. Thirty-third series. Pp. 304; illustrated. Philadelphia and London: J. B. Lippincott Company, 1923.

THIS number contains three articles on insulin, twelve on medical diagnosis and treatment, eight on surgery, and an obituary on Dr.

J. W. Ballantine. McPhedran and Banting's article on insulin, that on the diagnosis and treatment of allergic diseases by Leeuwen of Holland, and a description of the new disease toularaemia, by Francis, of Washington, D. C., will all appeal to the internist, while "Problems in Surgical Diagnosis, Pathology and Treatment," by Cumston, of Switzerland, is of interest from the surgical standpoint. On the whole, however, it must be said that this number is below the highest standard of *International Clinics*. A.

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THE DETERMINATION OF HYDROGEN IONS. By W. MANSFIELD CLARK, M.A., PH.D., Professor of Chemistry, Hygienic Laboratory, United States Public Health Service. Second edition. Pp. 480. Baltimore: Williams & Wilkins, 1922.

IN the second edition of this important work, the author has attempted to keep pace with the rapidly increasing literature on H-ion concentration. The discussion of acid-base equilibria has been accorded fuller treatment and expanded into two chapters. In Chapter V, a very extensive list of indicators has been introduced. More attention has been directed to the simple potentiometer and voltmeter arrangements, the use of which permits H-ion work, where cost prohibits the purchase of complete potentiometer outfits. Nevertheless, the author recommends the more precise instruments, so as to "keep the accuracy of measurement just ahead of immediate demands." New types of apparatus that have received mention are Gillespie's bicolorimeter, Goode's electron tube potentiometer, and the condenser-ballistic galvanometer system for measuring E. M. F. A mathematical treatment of oxidation-reduction potentials has been introduced, based on the more recent concepts of electron interchange. Biochemists should welcome the introduction of discussions of the Donnan equilibrium, cataphoresis, etc., although the subject of colloidal phenomena seems to have been rather neglected. The bibliography has been augmented to include more than 2100 references. O.

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PAPERS FROM THE MAYO FOUNDATION AND THE MEDICAL SCHOOL OF UNIVERSITY OF MINNESOTA, 1921-1922, Vol. II. Pp. 716, numerous illustrations. Philadelphia: W. B. Saunders Company, 1923.

THE second volume of collected studies from this celebrated foundation is made up of 107 different papers by almost as many authors. They are mostly based on theses presented by graduate

students toward advanced degrees, and are mostly presented in abstract. Nevertheless, a high scientific level has been maintained and much valuable information afforded. The papers are presented under the 11 headings: alimentary tract; urogenital organs; ductless glands; blood and circulatory organs; skin and syphilis; head, trunk and extremities; brain, spinal cord and nerves; organic and physiologic chemistry; general bacteriology; general miscellaneous; technic.

K.

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EPIDEMIOLOGY AND PUBLIC HEALTH. A TEXT AND REFERENCE BOOK FOR PHYSICIANS, MEDICAL STUDENTS AND HEALTH WORKERS. IN THREE VOLUMES. VOLUME II, NUTRITIONAL DISORDERS, ALIMENTARY INFECTIONS, PERCUTANEOUS INFECTIONS. By VICTOR C. VAUGHAN, M.D., LL.D., Emeritus Professor of Hygiene in the University of Michigan; assisted by HENRY F. VAUGHAN, M.S., DR. P.H., Commissioner of Health of the City of Detroit, and GEORGE T. PALMER, M.S., DR. P.H., Epidemiologist for the Department of Health of the City of Detroit. Pp. 917; 53 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS second volume of Vaughan's "*Epidemiology and Public Health*" is of equal interest with the first one and demonstrates the author's conception of the wide range of the subject. Many will be surprised at the large number of diseases included, those due to vitamine insufficiencies, the various food poisonings (bromatotoxismus) and goiter as well as various intestinal affections, including the parasitic infestations, malaria, filariasis, yellow fever, the trypanosomiasis, the kala-azars, tetanus, verruga peruviana, Japanese river fever, tularemia, trench fever, phlebotomus fever and numerous others. The historical sketches are particularly illuminating and quite complete, and the symptomatology in many instances is much more adequately presented than even in most of the recent systems on medicine.

M.

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DIE MEDIZIN DER GEGENWART IN SELBSTDARSTELLUNGEN. Edited by PROF. DR. L. R. GROTE, Privatdozent an der Universität Halle. Vol. I. Pp. 227; 6 illustrations. Vol. II. Pp. 250; 8 illustrations. Leipzig: Felix Meiner, 1923.

THESE are the first two volumes of a series attempting to present the living history of contemporary German medicine by proceeding "from the person to the subject." Of the six "autoergographs" of the first volume (Hoche, Kummell, Marchand, Martius, Roux,

Wiedersheim) and the eight of the second (Barfurth, Grawitz, Hùeppe, H. H. Meyer, Penzoldt, Rosenbach, Schultze, Schultz), only three or four can be said to have acquired more than a national reputation. How different from the names that could have been gathered a generation, or even ten or twenty years ago! In the similar series on philosophy, the contributors are said to be "aware of a certain embarrassment in speaking of themselves. They are overanxious to avoid self-advertisement. 'Americanism' (sic) is discounted." This embarrassment does not seem to have proved much of an obstacle to the authors of this volume. One cannot help being reminded of such projects as "Lives of Eminent Citizens of Squedunk County. Please write your own notice and inform us how many copies you want for distribution among your friends." It does not seem to the reviewer that Germany's attempts to regain her lost leadership in the world of science are furthered by such publications. There is some consolation in the fact that the "tadelloses, holzfreies Papier" will not long withstand the ravages of time.

K.

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PRACTICAL DIETETICS. By ALIDA FRANCES PATTEE, Graduate, Department of Household Arts, State Normal School, Framingham, Mass.; Former Instructor in Dietetics, Bellevue Training School for Nurses, Bellevue Hospital, New York City. Pp. 646. Fourteenth edition completely revised. Mount Vernon, New York: A. F. Pattee, 1923.

THE popularity of this book is attested by the fact that almost yearly editions have appeared since the initial number. The present edition, however, has been almost entirely rewritten so that in form and arrangement it is practically a new book. If the popularity of the previous editions is a criterion of the merits of the book, it may safely be said that the work is a splendid exposition of the principles of dietetics and of the practice of this most necessary adjunct to proper therapy.

M.

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CONTRIBUTIONS FROM THE PEKING UNION MEDICAL COLLEGE, PEKING, CHINA. Volume II, 1922. Peking, Peking Union Medical College, 1923.

THE second volume of the compilation of medical contributions to current literature from the pen of the various workers at the Peking Union Medical College is a very splendid example of what may be done by those working with enthusiasm and zeal even when handicapped by the obvious difficulties which are met with in a

semicivilized community, as we understand it. The contributions are catholic in their aspect; eye conditions, as would be expected, take up a goodly part of the work; but laboratory studies, parasitology and similar subjects are dealt with. In addition to the contributions of the local staff of the Peking School there are also included in the work the papers delivered at the dedication ceremonies of the Medical School in 1921. M.

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THE DOMINANT SEX. By MATHILDE and MATHIAS VAERTING. Translated from the German by EDEN and CEDAR PAUL. Pp. 289. New York: George H. Doran Company, 1923.

THE motive for this work is the effort of the authors to prove that either sex may be the dominant or the stronger one and that if either sex is truly dominant the characteristics which we know as feminine or masculine vary according to the sex which is the ruling one. Throughout their work by analogy with earlier races and the comparison of the animal kingdom they attempt to show that in those races in which the female sex is the ruling one, the male becomes entirely a subsidiary partner. The arguments of the authors are for the most part well taken. The reviewer does not feel that they have proved their main point, which is that in the course of the present civilization sooner or later there will come the equality of the sexes; the dominance of man over woman will no longer persist. In a criticism of the work it would seem that the whole force of the authors' arguments were invalidated by trying to show that in the animal kingdom the dominant sex is the female. It would thus seem that, as an incorrect statement of fact is one of their strongest arguments, others of their arguments may not be entirely true. M.

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OPTOTYPES. SEVENTEEN TEST LETTERS AND PICTOGRAPHS. By GREEN and EWING. Published by the C. V. Mosby Company, St. Louis, Mo., 1923.

THESE seventeen cards of test letters and pictographs for measuring the acuteness of vision, by Green and Ewing, are the very best and ideal of their kind.

Each card measures fourteen by seven and a half inches, making them very convenient for office use, especially so as each one is punched for binding.

The reviewer has no unfavorable criticism to make, but, on the contrary, recommends these valuable accessories, especially to those who do eye-testing in institutions for the deaf and dumb,



feeble-minded and illiterates. Therefore, these cards are not in every-day use in the office of the active ophthalmologist.

An immense amount of work and expense has been given by the authors and publishers, who are to be thanked for this contribution to ophthalmic science.

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ANNALS OF ROENTGENOLOGY. A SERIES OF MONOGRAPHIC ATLASES.

Edited by JAMES T. CASE, M.D., Ex-President of the American Roentgen-ray Society. Volume III. Digestive Disturbances in Infants and Children Roentgenologically Considered. By Charles Gilmore Kerley, M.D., and Leon Theodore Lewald, M.D. Pp. 81; 166 illustrations. New York: Paul B. Hoeber, 1923.

THIS is the third of the monographic atlases in the *Annals of Roentgenology* series, and it is divided into two parts. The first part, prefaced by a note on the Surgery of Infants, by Dr. William A. Downe, is a discussion of the digestive disturbances of infants and children. The second is made up of 117 roentgen-ray studies of the conditions mentioned in the first part. In these studies are included the history, the roentgen diagnosis, with the lesion or abnormality clearly indicated on the handsome illustrations, and the result of treatment.

This volume is a welcome and valuable addition to the relatively scarce literature of its kind, and one that truly fulfils its purpose as a diagnostic guide.

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Z.

PHYSIOTHERAPY TECHNIC: A MANUAL OF APPLIED PHYSICS. By C. M. SANSOM, M.D. Pp. 443; 85 illustrations. St. Louis: C. V. Mosby Company, 1923.

THIS book deals with the thermal, chemical, mechanical and electronic methods of treating disease and conditions resulting from disease and trauma. Indications for the use of and the technic of application of these modalities are discussed very thoroughly and in detail. While the author's claim of brilliant results in the treatment of locomotor ataxia, and that 'the treatment of hayfever by physical means comes near to being specific,' must be accepted with some reservation until the efficacy of these means has been more universally proved, the work contains much useful information, especially for those who are engaged in reconstruction work.

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# PROGRESS OF MEDICAL SCIENCE

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## MEDICINE

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UNDER THE CHARGE OF

W. S. THAYER, M.D.,

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AND

ROGER S. MORRIS, M.D.,

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**The Neutralization of Tetanus Antitoxin with Nucleic Acid.**—DOYON and DUFOURT (*Compt. rend. Soc. biol.*, 1923, 88, 1244) have discovered that nucleic acid is able to neutralize tetanus toxin *in vitro* within five minutes after the two substances are brought together in solution. If the mixture be injected before the five-minute period has elapsed, then some of the toxin is still active, its toxicity being inversely proportional to the time that has elapsed. Smaller quantities of the acid merely delay the tetanus and death. Protection *in vivo* is less effective, although death may be delayed, the prolongation of life depending on how closely the acid injection followed that of the toxin. Tartaric acid is less active in neutralizing the toxin, while sodium nucleate is entirely inactive. Nucleic acid precipitates the toxin and certain other elements from culture media.

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**Value of Phenoltetrachlorphthalein on Estimating Liver Function.**—PIERSOL and BACKUS (*Arch. Int. Med.*, 1923, 31, 623) describe a method of performing the phenoltetrachlorphthalein liver function test that adds considerably to its value as a clinical procedure. A duodenal tube is passed so that the tip rests in the second portion of the duodenum, and a steady drip from the outer end is initiated by aspiration and is maintained by having the patient drink a glass of water every half hour. The dye is injected as soon as a steady drip of bile-stained fluid is obtained, and the appearance time of the first dye is noted, as well as the time of its maximum intensity. Their principal contribution lies in their quantitative estimation of the amount of dye thus excreted by the liver for each half hour of a two-hour period following the injection. These estimations were made colorimetrically after first removing the

bile salts by precipitation and filtration. This quantitative feature of the test makes it, in the opinion of the authors, as useful in testing the functional capacity of the liver as is the phthalein test for the kidney. In a series of 50 cases tested, they found the delay in the appearance time of the dye to be proportional to the decrease in the output. In grossly pathologic livers the appearance time was twice as long as normal (23.2 minutes as compared to 11.6 minutes), and the dye output averaged but one-eighth of that in normal cases (2.71 mgm. as contrasted with 22.4 mgm.). This method substitutes the use of the duodenal tube in the place of withdrawing blood for examination to determine the dye excretion.

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**Amebic Bronchitis without Abscess.**—PETZETAKIS (*Bull. et mém. Soc. méd. d. hop. de Paris*, 1923, 39, 1229) reports 2 cases of pure amebic bronchitis. Each occurred in Egyptian males, laborers, in the fourth decade and was observed in the Greek Hospital of Alexandria. The symptoms were those of a mild bronchitis with cough and expectoration. The symptomatology was not characteristic in any way. The examination of the lungs showed no abnormality except the presence of rales, chiefly dry, which were somewhat generalized in one patient, localized about the angle of the left scapula in the other. There was no evidence of infiltration of the lungs, the liver was normal, there was no dysentery; one patient had had 3 to 4 stools daily for several weeks. The sputa were mucous, glairy, tenacious and streaked with bright red blood. In each case, actively motile *Entameba histolytica* were observed in large numbers, as well as the cysts. Both patients were promptly cured by intravenous and subcutaneous injections of emetin, 0.06 gm. The author has observed 3 more cases but they are still under treatment and are not reported here.

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**The Effects of Quinidine upon Paroxysms of Tachycardia.**—ILIÈSCU and SEBASTIANI (*Heart*, 1923, 10, 223) present a review of the reported cases of paroxysmal tachycardia—both auricular and ventricular—treated with quinidine, and report the results obtained in 2 cases of their own. They find that cinchona alkaloids are capable of slowing a heart which is affected by simple paroxysmal tachycardia. The action cannot, however, be looked upon as constant, as it failed to appear in 2 cases reported by Singer and Winterberg and in 1 of the author's cases. They believe it possible that the reaction would be constant were the doses of the drug increased. The preliminary slowing of paroxysmal tachycardia and the subsequent and abrupt transition to normal rhythm observed in many reported cases suggest that paroxysmal tachycardia may depend essentially upon circus movement, as do flutter and fibrillation. In cases responding favorably to quinidine, a single dose of 0.4 to 0.6 gm. by mouth has released the heart from the paroxysm. The transition to the normal rate is usually abrupt, though it may be gradual, as in the authors' case.

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**Diabetes and Insulin.**—In the discussion on this subject at the annual meeting of the British Medical Association, Section on Medicine, BANTING (*Brit. Med. Jour.*, 1923, 2, 446) gave the opening address, in which he recounted first the story of the research which led to the

preparation of insulin. He then takes up briefly the well-known facts about insulin; its preparations, in the laboratory, reduce the blood sugar to normal or less, render the urine sugar-free and by its means the depancreatized dog could be kept alive three times as long as without this organ. The clinical work has been done in Toronto by Graham, Campbell, Gilchrist and Fletcher, who find at the present time there is no fixed method of managing diabetic patients. Their habit is to admit the patient to the hospital for three weeks' training in routine and working out of tolerance if the case is at all severe. The patient is put upon the usual diet for twenty-four hours. He is then put upon a basal requirement diet of 4 grams of protein per kilo body weight. The remaining calories are made up of carbohydrate and fat in ratio of 1 to 1.3. This diet is continued for three or four days. In mild cases the patient usually becomes sugar-free. In the more severe the sugar output becomes constant. If the patient becomes sugar-free the carbohydrate is raised. If he could take 500 calories over and above the basal requirements insulin was not given. One unit of insulin is held to metabolize 2 to 2.5 grams carbohydrate, but this varied in different cases and in the same case at different times. The presence of infection required less. In mild cases one unit of insulin might metabolize 5 to 6 grams of carbohydrate. The initial dose should not be sufficient to make the patient sugar-free, five units usually being given to start with unless the patient is comatose. It is given an hour before meals and never more than once a day. By keeping the patient sugar-free on diet and insulin there apparently is a tendency on the part of the pancreas to produce insulin, as evidenced in many cases by the increased tolerance after insulin treatment, particularly in those cases adequately controlled by diet.

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## SURGERY

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UNDER THE CHARGE OF

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NORTHEASTERN HOSPITALS.

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**Space Compensating Function of the Cerebrospinal Fluid: Its Connection with Cerebral Lesions in Epilepsy.**—DANDY (*Bull. Johns Hopkins Hosp.*, 1923, 34, 245) says that in a series of operations for the relief of epilepsy a number of changes have been found with considerable uniformity. These are: dilatation of the ventricles, collection of fluid in the brain substance, softening of the brain in association with these collections of fluid, areas of induration in the brain (fibrosis or gliosis), changes in the meninges, and congenital malformations. It is believed that these are evidences of actual cerebral lesions (end-products of repair), and the frequency of the findings leads to the con-

clusion that there is a pathological basis for so-called idiopathic epilepsy in a large proportion of the cases. Confirmation of this view is obtained by means of ventriculography, which in a certain proportion of cases shows acquired or congenital distortion of the ventricles.

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**Studies on Tumor Formation (Heterotopic Tumors).—**NICHOLSON (*Guy's Hosp. Rep.*, 1923, 73, 298) says that an epithelial tumor is heterotopic only when some or all of its cells belong to a different histological type from that of the organ in which it has undergone its development. The best-known examples are found in the squamous-cell carcinomata of mucous membranes lined by glandular epithelium. Heterotopic cells constitute either the whole or only a part of the parenchyma of these tumors. Their histogenesis is to be explained by metaplasia, a de-differentiation, followed by an atypical re-differentiation of differentiated cells, and not by displaced cell-rests or other congenital malformations.

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**Köhler's Disease of the Tarsal Scaphoid.**—GREENWOOD (*Lancet*, 1923, 2, 205, 274) says that a history of trauma could probably be obtained in every case from parents of average intelligence, especially if the period inquired into is allowed to stretch as far back as two years. The author feels in the light of his own case that the child is subject to mild latent tuberculosis. This bone, being the keystone of the arch, is most subject to strains, stresses and blows. The early stage, evidenced by a rarefying osteitis, gives rise to such trifling clinical signs that no complaint is made and the disease usually escapes notice. When neighboring bones are involved, the case is diagnosed as frank tuberculosis of the tarsal bones. But should resolution occur and a reparative sclerosis take place either no diagnosis other than sprain or incipient flat foot is made, or a roentgen-ray examination is made and the condition found is called Köhler's disease. The author's case is a borderline case, since actual necrosis to a very limited extent had occurred.

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**Syphilis of the Stomach.**—LARIMORE (*Surg., Gynec. and Obst.*, 1923, 37, 133) says that gastric syphilis manifests a variable symptomatology, a chemistry and roentgen-ray findings that cannot consistently be of any other well-recognized gastric disease. The presence elsewhere of other undoubted signs of syphilis is a very large support to the diagnosis of syphilis of the stomach, and when absent great care must be used in making that diagnosis. Successful medical treatment is diagnostic only in early gastric syphilis. Restoration of normal gastric motility cannot be expected in well-advanced gastric syphilis. Surgery is indicated in late cases with permanent impairment of the gastric motor function. It is indicated by the clinical course and by the roentgen-ray findings. Resection of the prepyloric stomach is the preferred operation.

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**Tuberculosis of the Epididymis.**—MAXEINER and WALDSCHMIDT (*Minnesota Med.*, 1923, 6, 492) say that in a series of 15 cases, 10 showed extragenital tuberculosis before operation. The average duration of symptoms was nine and one-half months before operation. Pain, which is usually considered negligible, was present in 13 cases. In a

large majority of cases the first symptoms were noted in the lower pole. Two-thirds of the cases were of bilateral involvement. In one-third of the series, one testicle was so badly involved that it had to be removed. Eight cases report improvement, 7 are unchanged. Local anesthesia and primary closures were employed to prevent spread of involvement and sinus formation respectively.

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**Flow of Lymph from Ileocecal Angle and its Possible Bearing on the Cause of Duodenal and Gastric Ulcer.**—BRAITHWAITE (*Brit. Jour. Surg.*, 1923, 11, 7) says that cases showing actual and obvious pathological extension by direct lymphatic connection from the ileocecal angle to the region of the pyloric end of the stomach are numerous. A suggestive pigmented gland case was cited in full in the article. Moynihan in an abdominal operation found a mass of tuberculous glands in the ileocecal angle, a complete chain up to the third part of the duodenum, and in addition, a chain running along the common bile duct. A remarkable case was cited by Gordon Taylor, which developed symptoms of perforated gastrojejunal ulcer in the line of anastomosis of a previously performed gastroenterostomy. Operation revealed the perforation with a generalized peritonitis. As a part of a routine examination the appendix was examined, and found to be in the stage of acute gangrenous inflammation. This case would suggest infection of the posterior wall of the stomach from a flow of highly infected lymph.

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**Retrograde Intussusception of the Small Intestine after Gastroenterostomy.**—DRUMMOND (*Brit. Jour. Surg.*, 1923, 11, 79) says that retrograde intussusception of the small intestine is now a well-recognized complication following gastroenterostomy. Fourteen cases have been recorded. The type of gastroenterostomy performed has nothing to do with the occurrence of the ascending intussusception. In all probability the ascending intussusception is caused by too rapid emptying of the stomach, causing irritation of the jejunum and setting up of antiperistalsis. Diagnosis is straightforward and should, now that the condition has been recognized, be easily made. The history of a previously performed gastroenterostomy, often of many years' standing, followed by sudden griping epigastric colic, vomiting of blood, often a palpable tumor in the left hypochondriac region, with absence of rigidity, distention and acute tenderness, suggest the diagnosis. The treatment of the condition is immediate operation. A reliable preventive treatment has not been suggested.

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**Loose Bodies in Joints.**—HENDERSON and JONES (*Jour. Bone and Joint Surg.*, 1923, 3, 400) say that osteochondromatosis of the synovial membrane is one of the causes of osteocartilaginous loose bodies in the joints and probably the sole cause of the bodies in the bursæ and tendon sheaths. They believe that the condition should be classified as a benign neoplasm. Trauma is a secondary factor. One of the authors' cases was associated with a malignant chondrosarcoma in the lower end of the femur. No malignancy was discovered in the knee-joint. Removal of all the bodies relieves the patient in the majority of instances. Amputation or resection was not found necessary for synovial osteochondromatosis.

**Experimental Incision in the Cadaver for Drainage of the Ankle-joint.**—DAVID (*Jour. Bone Joint Surg.*, 1923, 3, 481) says that the ankle-joint may be divided into two compartments by an imaginary line passing transversely through the center of the malleoli. The posterior compartment is formed by the posterior surface of the trochlea, the anterior being formed by the relaxation of the anterior ligament over the neck of the astragalus. Experimental work on a number of cadavers proved that the posterior external approach was a reliable and safe one. The joint cavity is easily accessible by this route, and with the foot dorsiflexed to a right angle, evacuation of the fluid was complete.

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**An Electrochemical Interpretation of Shock and Exhaustion.**—CRILE (*Surg., Gynec. and Obst.*, 1923, 37, 342) says that there is much evidence in support of the conception that man and animals are electrochemical mechanisms constructed on the pattern of the constituent cells, each one of which in itself is an electrochemical mechanism. The author outlines the various electrical principles and phenomena noted in cellular physiology. The nucleus is positive, the cytoplasm negative. The brain as compared with the liver is positive. By his hypothesis the brain is the positive pole, the liver the negative, the connecting lines the nerves, the salts in solution, the electrolyte. Sleep is interpreted as a period of recharging of batteries decreased by activities of the day. The theory would interpret that there is no surgical shock when the state of negativity is maintained by the exclusions of stimuli.

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**Renal Hemorrhages (Postoperative).**—JIANOU (*Jour. d'urologie*, 1923, 15, 350) says that the conservative operation of nephrotomy is not without danger or complications. There are two varieties of bleeding after this operation: primary, occurring within several hours of operative procedure, which is arterial in character; and secondary hemorrhage, occurring six to twelve hours after operation, which is either venous or arterial in nature. Several authors are quoted who think infarct with subsequent processes of infection are the causal factors in late hemorrhages. The author thinks that the hemorrhages are due to section of intrarenal vessels, with infection as a sequel. He recommends the deep lock-stitch suture through the entire area sectioned.

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**Brain Abscess.**—KEEN (*Arch. of Surg.*, 1923, 7, 297) says that brain abscess in general is difficult of treatment: Abscess of the frontal lobe of the brain has been recognized before death in only about one-half of the reported cases. The high mortality indicates the need of a more careful study of such cases. Persistent headache with sustained leukocytosis and especially the presence of retinal changes indicative of pressure in cases of drained frontal sinusitis or ethmoiditis indicate exploration. Exploration by the two-stage operation through a sterile field may be indicated. Direct drainage with a minimum trauma should be established and should not be discontinued until all symptoms have subsided. It is of paramount importance to drain a brain abscess for too long rather than too short a time.

**The Transfusion of Unmodified Blood.**—BRINES (*Arch. Surg.*, 1923, 7, 306) says that a greater degree of care and accuracy should be exercised in choosing donors. Sodium citrate is harmful chemically, biologically, and physically in blood transfusions, and some fatalities have followed its use. Reactions are fewer and milder following the whole blood method than following the citrate method. The Unger method seems to be the most simple and most generally successful for the giving of blood directly. This method ensures promptness, as no time need be consumed by preliminary details or arrangements. With the proper listing of professional and semiprofessional donors, it should be possible to perform a direct transfusion in any part of a large city, within notice of one hour.

**Upon Operation for Ischiorectal Fistula.**—KIRCHMAYR (*Zentralbl. f. Chir.*, 1923, 25, 993) outlines the faults and direful complications of fistula operations, with incontinence of gas and feces. The author's experience had been first to spare the sphincter, and if cut, to reunite it by suture. In removing the fistulous tracts, especially when attended by marked infiltrate, the wounded areas healed and filled with granulations extremely slowly. Fat-flaps were dissected out and inserted into the cavity. Very excellent results followed these measures. The author has found the fat-flaps useful in separating concomitant fistulæ of the rectum and vagina.

## PEDIATRICS

UNDER THE CHARGE OF

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OF PHILADELPHIA.

**A Seasonal Tide of Blood Phosphates in Infants.**—HESS and LUNDAGEN (*Jour. Am. Med. Assn.*, 1923, 79, 2210) have made a most interesting investigation to show this. In their series during 1921 in the summer the phosphate content of the blood was 4.34 mg. per cent, which is within the normal for the Bell and Doisy method. Further data were not available for 1921 until December when it was found that the average had fallen to 3.92 mg. per cent. Monthly examination, some 300 in all, on 60 infants, demonstrated a steady decrease of the inorganic phosphate content, the lowest ebb being in March. This level would have been still lower had it not been for the fact that whenever the phosphate content was found to be as low as 3.75 mg., the child was given either sun treatment or irradiation from an artificial source. It was found that the blood test furnished a valuable criterion as to when heliotherapy should be instituted. In April the tide began to rise, ascending markedly during May, and rising to almost a normal level during June. It seems probable that this seasonal tide with its summer flood and winter ebb occurs to a greater or to a less degree in most bottle-fed babies living in large cities. These babies were outdoors every fine day bundled up in the usual manner with only the



faces showing. Their diet was far better than the average. The authors are unable to state how breast-fed babies react to tidal blood variation. They believe however that these also show a seasonal variation from the fact that 50 per cent of well nourished breast-fed babies coming to their clinic show clinical evidence of rickets at the end of March. The seasonal variation evidently indicates that the chemical constituents of our blood is not constant for all periods of the year. This probably holds true of other tissues. Marked fluctuations of this character may be discovered only in young children, in whom the body has to make provision not only for metabolism associated with maintenance, but also for that demanded by rapid growth, a mechanism which necessarily involves a tendency to wider deviations from the normal. It is quite possible that the phosphate blood tide is only one of the many seasonal variations that take place in the body. Undoubtedly climatic conditions exert a pronounced influence on general nutrition. It is also quite possible that chemical alterations of the tissues, induced by seasonal meteorological variations, may exert an influence not only on nutrition but also on infection. The low content of inorganic phosphate that occurs in early spring and is closely associated with rickets may play a role in the susceptibility to infection which accompanies this disorder. Seasonal alterations of the blood may bear a relationship to the vagaries of incidence of the epidemic diseases.

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**The Mechanism and Fundamental Causes of Epilepsy.**—ROSETT (*Arch. Neur. and Psychiat.*, 1923, 9, 689) found in his investigations that a physiologic reaction in normal man and animals exists, composed of the following connected train of phenomena: a temporary reduction, disintegration or extinction of the cerebral functions; a tonic contraction of the entire skeletal musculature, with a certain predominance of the extensors, adductors and pronators; the consequent fixation of the joints resulting in the posture characteristic of the state of decerebrate rigidity; clonic muscular contractions or alternating contractions of antagonistic groups of muscles; recovery, marked by symptoms of integration of the disintegrated cerebral functions and a state of general exhaustion. This reaction occurs on exposure to the action of a stimulus requiring sudden movement on the part of the organism, or the narrow focussing of attention and in connection with certain functions such as sleep, defecation, sneezing, coughing, parturition. The mechanism of this reaction is to be found in certain anatomic structures and physiologic functions underlying the production and distribution of muscle tonus in the nervous system. The biologic purpose of the reaction is the automatic fixation of the relatively distal segments of the body and limbs. The reaction is characterized by a periodicity of occurrence. The phenomena which constitute the normal reaction described being in a great number of particulars the same as those which constitute the epileptic paroxysm, might be suitably called the normal epileptoid reaction. This is elicited with greater ease under the influence of the same agencies which cause an exaggeration of the epileptic paroxysm. An example of such an agent is caffeine. On the other hand, influences which tend to hold the epileptic reaction in abeyance, such as bromides and phenobarbital, have the power to diminish the manifestations of the normal epileptoid reaction. Any factor, which operates

permanently to cause large periodic suspensions of the highest nerve functions, whether that factor be a brain tumor, a poison in the blood, a peripheral irritation on an inherited defect will tend to bring about the clinical picture of the epileptic paroxysms.

**The Treatment of Acute Poliomyelitis.**—ADCOCK and AMOSS (*Jour. Am. Med. Assn.*, 1923, 81, 474) report a case of poliomyelitis in which they used intravenous injections of hypertonic solution and convalescent human serum intraspinally. In former experiments they found that monkeys given convalescent human serum intraspinally or intravenously and hypertonic salt solution intravenously showed marked improvement as compared to controls. By the shrinking of the central nervous tissues after intravenous injection of hypertonic salt solution more space is available in the subarachnoid space for the reception of large amounts of convalescent serum. This is an advantage as the serum is at best weak in antibody content, and correspondingly large amounts must be injected. The beneficent effect of the change of the tonicity of the blood with the marked decrease in the volume of the brain and spinal cord, is to reduce the inflammatory edema of the cord. Their experiments have not advanced sufficiently to warrant the statement that edema is entirely due to osmosis. The main possibility of the beneficent result of this method lies in the fact that the intravenous injection of hypertonic solution brings about an aspiration of serum from the subarachnoid space into the perivascular system, thus ensuring a more intimate contact between the main lesions of poliomyelitis and the serum, which can be regarded as a distinct advantage in local specific therapy. There is another possibility in connection with the employment of this method. It is possible to administer enough hypertonic solution, approximately 1 gm. of sodium chloride per kilogram of body weight, to cause cerebrospinal fluid pressure to fall from 120 mm. of water to 90 mm. of water without damage. This loss of fluid within the central nervous system is replaced afterward by an increased passage of fluid from the blood stream to the cerebrospinal fluid, normal pressure being restored within a few hours. On the hypothesis that this increased flow of fluid would facilitate the passage of serum from the circulation to the fluid spaces of the central nervous system, the intravenous injection of immune serum one or two hours after the injection of the hypertonic solution is recommended. The case reported conforms to the type of Landry's paralysis seen in epidemics. In such a case the prognosis is usually grave. Whether the intravenous injection of hypertonic salt solution stayed or slightly cleared the edema of the cord, or brought the convalescent human serum nearer the site of inflammation, or only made it possible to inject more serum intraspinally without danger of pressure, is not clear.

**Health and Nutrition Work among Children of the Preschool Age.**—BACON (*Atlantic Med. Jour.*, 1923, 26, 606) at the Starr Center Dispensary has found that the Woodbury or Baldwin tables are at present the best indices of nutrition for children between the ages of two and six years. Ideal standards must be established. Once these are decided upon, measurements of various groups of children must be made

according to standard regulations. The class method combined with personal interviews with those in the class has given encouraging results with children of the preschool age. The success of a class depends largely upon the ability and the ingenuity of the doctor and his assistants. Evidence of value of nutrition work among children of the preschool age are shown by the formation of health habits which stand the test of time; by signs of physical improvement such as the correction of defects, as correction of heart action, correction of constipation, gain in weight and height, and decreased tendency to become ill; and a definite tendency on the part of the child to adapt himself to a social and hygienic environment.

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**The Value of the Toxin (Antigen) of *Rhus Toxicodendron* and *Rhus Venenata* in the Treatment and Desensitization of Patients with Dermatitis Venenata.**—STRICKLER (*Jour. Am. Med. Assn.*, 1923, 80, 1588) says that in the treatment of dermatitis venenata due to poison ivy or poison oak, the toxin (antigen) method of treatment constitutes the best method of procedure. Counting the unsuccessful and doubtful results in his series of 356 cases, there were noted 19 cases, slightly more than 5 per cent, in which failure or only slight improvement resulted. These results were obtained without the additional use of local applications. Relief was obtained in twenty-four hours after the institution of the treatment. Only occasionally, and then in very severe or generalized cases, does a forty-eight-hour interval elapse before relief is obtained. Cure is obtained within from four to five days after the institution of the treatment. In the desensitization of highly susceptible patients the results seemed to be encouraging. While this series was not sufficiently large to arrive at positive conclusions, the results were sufficiently satisfactory to at least warrant a trial in such individuals. The method of desensitization is a rational one, and it is based on the principles that have been successfully applied to the desensitization of other disease conditions. Considering that in the past no hope of prevention could be held out for these constant sufferers from poison ivy, and realizing the great suffering and dread that these patients undergo, there seems to be more than an ample justification for the employment of this method of desensitization. The treatment is simple and can be carried out with ease, and if future results justify past experiences, this treatment should prove a great blessing to the susceptible persons. The method is a combination of intramuscular and oral administration.

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## OBSTETRICS

UNDER THE CHARGE OF

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**Repeated Dystocia from Fetal Anomaly in Successive Pregnancies.**—McDONALD (*Am. Jour. Obst.*, 1923, 6, 82) describes a remark-

able case where a patient had transverse position and the same abnormalities in the fetus in successive pregnancies. The mother's age was twenty-eight years, and for two generations the family history gave no record of the birth of a deformed child. Before coming under observation she had two pregnancies resulting in premature labor, one child living but a few hours, the other stillborn. The statement is positively made that there was no external deformity in either of these children. There was no history of previous infection or acute disease in the mother, and the Wassermann reaction in husband and wife a year previously had been negative. Pregnancy proceeded until about the seventh month, with great distention of the abdomen and evidence of excessive fluid. At labor a small foot protruded with six toes. On endeavoring to extract the fetus the abdomen was found so enormously distended that it was necessary to rupture the abdominal wall of the fetus, when a very large quantity of clear fluid was expelled. A small fetus was easily extracted. There was practically no amniotic liquid. There was transposition of viscera, abnormality of the bladder and hydrocephalus. About two years later, the same patient gave a 1+ Wassermann reaction. She was treated with arsphenamine and mercury. At three months' pregnancy there was bleeding and pain with the discharge of no mass or clots, and pregnancy went on until heart sounds were heard and movements were felt. At about seven months labor developed; birth was accomplished with the head extended, brow presentation, face anterior. The child died soon after birth. On examination, the same abnormalities essentially were present which were found in the preceding pregnancy. The sex of the second child differed from that of the first. This case presented four types of abnormality: (1) The unusual number of fingers which were webbed; (2) transposition of viscera; (3) abnormal development of the urinary tract with hypertrophy of the bladder wall and patent urachus; and (4) dropsy. So far as the condition of the fingers is concerned, this has been traced in some families through four generations. As regards the frequency of malformation, it has been estimated that spontaneous abortion occurs in 20 per cent of all pregnancies. In all abortions from 40 to 60 per cent are associated with a pathological condition in the product of conception. Such abnormalities occur during the first two months of pregnancy, before the development of the placenta is complete. Under these conditions but 1 in 12 of the impregnated ova can be carried to full term, and when pregnancy is so prolonged it produces a monster with varying degrees of abnormality. Where the pregnancy is tubal the occurrence of abnormalities in the ova may reach 96 per cent. Where there is a shortened spontaneous abortion during the first two months of pregnancy it should occasion a suspicion that there is something wrong with the ovum, which, if carried to term, may result in the birth of a monster. This is sometimes caused by abnormal implantation of the ovum in a defective or abnormal decidua, and in a mammalian ovum these abnormalities may develop before implantation occurs. From this it results that the growth and development of certain tissues in certain regions are delayed at a critical time, while other tissues not so affected grow disproportionately and the normal relationship is lost. This produces abnormality which

may destroy the fetus and bring on abortion, or may be so slight that the fetus may go on to full term, becoming some sort of monster. There is a well-marked tendency for the same mother to produce such offspring in repeated pregnancies.

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**A Successful Test for Liver Function in Pregnancy and its Toxemia.**—ROSENFELD and SCHNEIDERS (*Jour. Am. Med. Assn.*, March 17, 1923, 80, 743) describe a test which they have perfected and applied to a considerable number of patients normally pregnant and also in the toxic condition. The description of the test is technically interesting to chemists. The principle upon which it is made consists in injecting a dye into a vein after removing a small quantity of blood to serve as a control. The arms are used for the experiment, very small quantities of blood are drawn from a vein in the opposite arm at intervals of fifteen minutes, one hour and two hours after injections; these various samples of blood were then studied. The chemical agent employed was phenoltetrachlorophthalein; 5 mg. of the dye for each kilogram of body weight was used. The result of this study showed that cases of normal pregnancy have a curve coinciding with that of normal non-pregnant cases. This suggested that the so-called liver of pregnancy has no actual impairment in function. Cases of toxemia including eclampsia showed a definite relationship between the degree of liver impairment as measured by this test and the degree of toxicity as shown by the clinical picture. The results obtained in several cases suggest that this test may furnish a more accurate index of the existent toxicity than variable clinical symptoms and that by this test the obstetrician may be able to anticipate the clinical picture in forming an opinion regarding the degree of toxicity present at a given time. The toxemias of pregnancy show definite liver impairment and if the toxemia be relieved there is a return of normal liver function. The test gives a quantitative index of the functional capacity of the liver and should be of service in determining the necessity for the interruption of pregnancy.

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**Pregnancy and Labor After the Operative Replacement of the Inverted Uterus.**—TEUFIK (*Zentralbl. für Gyn.*, 1922, 46, 1956) describes the case of a woman aged twenty-eight, whose first labor had terminated naturally. The second labor was also spontaneous, but the midwife pulled strongly upon the umbilical cord and inverted the uterus. Later the patient came to hospital, suffering from anemia and its result. The uterus was found inverted. It was replaced by Küstner's method, followed by prompt recovery. The patient left the hospital in good condition. Menstruation was regular and painless for six months after, and then the patient came to the hospital five months pregnant. She was suffering no inconvenience and was ordered an abdominal bandage and advised to abstain from violent motions. Pregnancy went on and the patient finally gave birth spontaneously to a male child fully developed at term. The placenta was also spontaneously expelled, but there was more than usual hemorrhage afterward. Mother and child made a good recovery. Spontaneous labor after inversion of the uterus and its cure by operation is of rare occurrence.

**Injury in Labor to the Brain of the Newborn.**—SCHWARTZ (*Zentrabl. für Gyn.*, 1922, 46, 1965) has found that in newborn children under five months 65 per cent show some injury to the brain. These results are characteristic and typically placed and illustrate the influence of parturition upon the central nervous system. Most important are large hemorrhages into the cerebral substance and into the pia mater. When the veins are studied, instead of terminating in small branches, they end in wide blood channels in various portions of the cerebral substance. If these children survive their birth, lesions remain as the result of the hemorrhage. Areas of necrosis often develop in the brain substance. On microscopical examination, the lesions are best seen in the nerve fibers of the brain and in the axis cylinders. The whole picture is that described by Virchow as encephalitis of the newborn. So far as statistics are concerned, in 10,000 births 950 children would perish by the end of the first month. Of these 230 would show some injury to the brain, although a clinical diagnosis might have been made of asphyxia, congenital weakness, atrophy, or other condition as the essential cause of the death.

**Prenatal Care.**—ROBINSON and others (*Brit. Med. Jour.*, 1922, 2, 1174) contribute their experiences upon the value of prenatal care. The mortality of the newborn arises from hemorrhage and accidents in birth, from the toxemias of pregnancy, septic infection and pre-existing or intercurrent disease. In general hospitals disease is most important; in maternities the hemorrhages and accidents of labor, and in the houses of patients septic infection. Prenatal care is most valuable in preventing toxemia, eclampsia and the accidents of labor. Routine examination during pregnancy should greatly diminish the mortality of the newborn. It was thought that such previous study of cases should reduce the application of forceps in labor to less than 3 per cent, and have a correspondingly good effect upon other conditions.

## GYNECOLOGY

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**Relation of Cell Type to Degree of Malignancy in Cancer of Cervix.**—The hypothesis under which MARTZLOFF (*Bull. Johns Hopkins Hosp.*, 1923, 34, 141) began his interesting study on cervical cancer was that if basal cell cancer with its relatively low grade of malignancy exists on epidermal surfaces of the body elsewhere, why should it not occur

in the cervix uteri and warrant an equally favorable prognosis? He felt that the epidermal integument of the cervix differed morphologically in no essential way from skin except for the absence of a stratum corneum, dermis, dermal glands and dermal appendages. In short, why should epidermoid cancer of the cervix differ from epidermoid cancer occurring in other situations? The object of his study, therefore, was to discover, if possible, whether in this large and common group of epidermoid or squamous cell carcinoma of the cervix the histomorphology of the predominant types of cancer cells might signify anything relating to the malignancy of the disease. Because of the relatively poor prognosis as to an eventual operative cure which can be given in these cases, it was thought that any information such an investigation might afford would be of definite value and for this purpose data were gathered from the records of 387 patients in the wards of the Johns Hopkins Hospital prior to the year 1920, including only those cases in which there were complete records together with all pathological material. The study showed that the cells seen in epidermoid cancer of the cervix fall morphologically into three large groups: transitional, fat spindle and spinal cell groups. No epidermoid cancer of the cervix was encountered which conforms to basal cell cancer of the skin in regard to its apparent lack of malignancy. The histomorphology of the predominant types of cells in epidermoid cancer of the cervix is important in that it indicates the relative malignancy of a given type of tumor. In this study the spinal cell type of cancer proved to be the least malignant, the transitional cell type is next in order of increasing malignancy and the fat spindle cell type of cancer has proved to be the most malignant of all. The adenocarcinomata, as far as relative malignancy is concerned, fall in between the spinal cell and transitional cell groups of epidermoid cancer. The presence of epithelial pearls is significant only when they are associated with cancers of the spinal cell type and then they appear to indicate a lessened malignancy of the cervical new growth. Aside from these interesting observations on histology in its relation to malignancy there were several other interesting features from a statistical standpoint which this study brought forth. For example, the vaginal mucosa was involved in over 50 per cent of all the carcinomas of the cervix in the series, irrespective of the extent of the cervical involvement. Secondary involvement of the corpus uteri in cervical cancer occurred in 41.3 per cent of the cases in which the entire length of the cervix was involved. One-third of all the patients seen during the first six months of symptomatic disease, with the exception of those suffering from the spinal cell type of cancer, had extension of the neoplastic process to the broad ligament, while less than 10 per cent of the patients with broad ligament involvement lived more than one year after operation. The first symptom of disease in almost 85 per cent of the cases was some form of unusual vaginal bleeding, while in 97 per cent of the cases some form of unusual vaginal discharge (either bleeding or leukorrhea) was the primary symptom. Of all the cancers in the series 52.1 per cent occurred between the ages of thirty-six and fifty years inclusive. Of the patients between thirty-one and thirty-five years inclusive 18.6 per cent are living and well, which is the highest "cure" incidence for any five year age-period in the study. In 58.8 per cent of the patients operated upon where broad

ligament induration was noted on physical examination, this finding signified carcinomatous extension. The total operability of the cases in this study was 46.5 per cent while the total operative mortality was 14.2 per cent. The operative mortality prevailing in their clinic at the present time however is between 6 and 7 per cent. The incidence of "cures" is almost twice as frequent in the cases treated by abdominal panhysterectomy as compared with those treated by vaginal panhysterectomy. Preliminary curettage performed several days prior to the radical operation for cancer was the procedure employed in 36.8 per cent of the patients who are now living and well. From this Martzloff concludes that a diagnostic curettage not immediately followed by a radical operation does not by any means render the prognosis hopeless. The incidence of so-called "five year cures" in this series is 26.6 per cent.

**Modification of Rubin Technic for Tubal Inflation.**—The modification of the Rubin technic which has been suggested by JACOBY (*Surg., Gynec. and Obst.*, 1923, 36, 571) consists essentially in the substitution of a Janet Frank syringe for the tank of gas with its attached reducing valve and flow volumeter and the injection of air instead of oxygen or carbon dioxide. One may use any other suitable means for the introduction of air, such as a rubber bulb. The method of performing the test is as follows: With the patient in the dorsal position the bivalve speculum is introduced. The cervix and vagina are wiped dry with cotton and painted thoroughly with tincture of iodine. The cannula is introduced into the cervix past the internal os. The urethral tip on the cannula is pressed against the external os and acts as an obturator and prevents the regurgitation of gas. A tenaculum for grasping and steadying the cervix is as a rule unnecessary, for it is usually easy to introduce the cannula without it, doing away with the pain attendant on its use, and slight pressure on the cannula serves to hold the obturator firmly against the external os. The cannula is now connected by means of rubber tubing and a T-tube connection to a spring manometer on the one arm and a Janet Frank syringe with the plunger drawn out to its fullest extent on the other. Air is gently introduced through the cannula by pressure on the plunger of the syringe. The pressure exerted is recorded on the manometer. A pressure of 220 mm. mercury is the maximum permitted, and if the air will not flow at that pressure maintained for a little while, the tubes are considered closed. In such cases retests are made one or two weeks later. The usual initial pressure varies from 60 to 120 mm. mercury with a fall of pressure when the initial resistance is overcome and the air is flowing. It has been found that it is sufficient to introduce from 50 to 75 cc of air. There is no immediate reaction. Varying from a few minutes to half an hour after the patient assumes the upright position, there is a pain felt in the upper part of the abdomen and later in one or both shoulders, more commonly in the right. This pain lasts with diminishing intensity for about two days, the duration depending upon the amount of air introduced, but at no time seriously inconveniencing the patient. No other reaction occurs. This procedure has been used in 40 cases with no evidence of any serious result, such as infection. Nor is there any reason to expect it, as the result of the introduction of air, since in every



laparotomy air enters the peritoneal cavity with no untoward results. All the instruments used are of course sterilized. The advantages of this modification in technic are obvious. It eliminates the necessity of having on hand cumbersome tanks of gas with their attachments. There is no possibility of the air being exhausted, as occasionally happens with a tank when a test is in progress. Being more compact the apparatus is readily portable and there is no expense and inconvenience in the replacement of tanks. Air is free and always obtainable. The slight increase in the duration of the reaction can hardly be considered a big drawback, since it never amounts to a very great discomfort and can be regulated by the amount of air introduced.

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## PATHOLOGY AND BACTERIOLOGY

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**Types of Canine Anaphylaxis.**—According to MANWARING, CHILCOTE and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 274) the typical anaphylactic reaction in dogs is characterized by a sudden, pronounced fall in arterial blood-pressure which is reduced to about 25 mm. Hg, by the end of ninety seconds and is demonstrable in virtually all dogs tested from eighteen to twenty-four days after intravenous horse serum sensitization, with recovery usually in from one to two hours, depending upon the severity of the reaction. The authors have encountered another type of canine anaphylaxis, which occurred in a dog tested during the seventh week of horse serum sensitization and in which a gradual and irregular fall in the arterial pressure began four minutes after intravenous serum inoculation, death occurring in nine and one-half minutes. The lungs were found to be almost non-collapsible, but could be readily collapsed on pressure, the partial pulmonary fixation passing off in about fifteen minutes. The blood became non-coagulable by the reaction, but slight hepatic changes were observed and no duodenal hemorrhages could be seen. The picture of this latter type of reaction resembled that encountered in guinea-pig anaphylaxis.

**On Isohemagglutination.**—DYKE (*Brit. Jour. Exper. Path.*, 1922, 3, 146) conducted a series of experiments consisting in the absorption of the three agglutinating sera, those of Groups II, III and IV; by the three agglutinable types of corpuscles, those of Groups I, II and III. The sera used were usually a day to a week old. The corpuscles were collected in 2 per cent sodium citrate solution in normal saline, washed

three times in normal saline and suspended in the same fluid. It was found that the age of the corpuscles made very little difference in their activity. For absorption five drops of a 50 per cent suspension of corpuscles in normal saline were added to five drops of the serum to be tested, and left standing, either overnight at room temperature, or in the incubator at 37° C. for two hours. On completion of absorption the mixture of corpuscles and serum was shaken up and centrifuged. The supernatant fluid was pipetted off and tested as to its remaining agglutinating power. The absorption tests performed on sera of Groups II, III and IV, using corpuscles of Groups I, II and III, confirmed von Dungern and Hirschfeldt's hypothesis as to the distribution and nature of agglutinins and agglutinable factors in the four blood groups. It was further found that the sera from different individuals of the same group varied in their agglutinating powers. The relative titer of the two agglutinins in any given Group IV serum may be equal or very unequal, and corpuscles from different individuals of the same group could vary as to their agglutinability by the same serum. The relative degree to which the agglutinable factors may be present in corpuscles from any individual belonging to Group I varied greatly, while corpuscles from different individuals belonging to Group I differed in this respect. As a result of his observations the author believes that a quantitative estimation of the agglutinin titer should be made before any serum is selected for grouping purposes and only those sera should be used which show agglutinating power up to a dilution of at least 1 to 10.

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**A Hitherto Undescribed Pair of Isoagglutination Elements in Human Beings.**—Landsteiner, in 1901, discovered three human blood groups, and soon afterward, Decastelli and Sturli found the fourth group. Landsteiner recognized the existence in human serum of the presence of two isohemagglutinins, and two isoagglutinable substances in the corpuscles. Recently, Guthrie and Huck reported the discovery of a third pair of isoagglutination elements. In the course of a class demonstration of the two original pairs of isoagglutination elements, as described by COCA and KLEIN (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 466), the serum of Doctor Coca—a Group I individual—was absorbed first with the washed corpuscles of a Group II person and then with the washed corpuscles of a Group III individual. The supernatant fluid, after these absorptions, no longer clumped the corpuscles of the respective Group II and Group III individuals but still possessed a vigorous power of agglutinating the corpuscles of a Group IV person, which were agglutinable by the serum of the Group II and Group III individuals. This observation indicated the presence of another pair of isoagglutination elements. Examination of ten other Group I sera revealed the presence of a new isoagglutinin in 7 of them, whereas it was present in 2 of 6 Group III sera. The possibility of this pair of isoagglutination elements being identical with that described by Guthrie and Huck must be considered as indicated by the authors.

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**A Dangerous "Universal Donor" Detected by the Direct Matching of Bloods.**—LEVINE and MAYBEE (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 468) recount an interesting and important observation having

to do with the advisability of employing the "universal donor" Group I (Jansky) or Group IV (Moss). Their account is quoted: "In cases of transfusion where it is difficult to obtain a donor of the same group as the patient, a person of Group I (Jansky) has been considered suitable on account of the fact that the corpuscles of this group are inagglutinable by the isohemagglutinins. The fact that the plasma of a Group I individual contains isoagglutinins capable of clumping the corpuscles of the recipient has been ignored, because, under ordinary circumstances, the quantity of the plasma transfused is too small to affect the larger proportion (five to ten times) of the recipient's corpuscles. In carrying out the method of the direct matching of bloods as described by Coca, we found that the plasma of one of us (M., Group I) produced complete agglutination of ten volumes of the corpuscles of P. L. (Group II). Quantitative tests in the test tube showed that moderate agglutination of P. L. corpuscles was produced by as little as 1/20 volume of the M. plasma. This observation reveals a risk in using a member of the so-called "universal donor" group for the first time without making a rough quantitative estimation of the agglutinating power of the individual's plasma. It is advisable, therefore, in carrying out the direct matching according to Coca, to include a mixture of equal parts of undiluted recipient's citrated blood with the donor's citrated blood, diluted 1 to 5.

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**The Endothelial Factor in Anaphylaxis.**—MANWARING, CHILCOTE and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 273) found that if the lungs of a normal dog are perfused with Locke's solution, followed by Locke's solution containing 0.25 per cent to 1 per cent horse serum, no recognizable pulmonary reaction took place, the rate of perfusion flow remaining constant, the lungs collapsing normally on releasing the tracheal clamp and no frothy fluid escaping from trachea. If, however, the lungs of a sensitized dog were similarly perfused, a marked pulmonary reaction occurred. This reaction was characterized by a 75 per cent reduction in the rate of perfusion flow, which reached its maximum by the end of two minutes, with slight tendency to recover after three minutes; an increase in size and consistency of the lungs, with non-collapse on release of tracheal clamp and the escape of large quantities of fluid from the trachea on releasing this clamp. The authors believe that the increased capillary permeability is the most significant feature of these reactions and that 'increased specific capillary permeability will ultimately be shown to be the dominant fundamental factor in protein sensitization, to which all other anaphylactic phenomena are secondary.'

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**Anaphylactic Reactions on Isolated Canine Organs.**—When they perfused the isolated organs of horse serum sensitized dogs with Locke's solution containing 0.5 to 1 per cent horse serum, MANWARING, CHILCOTE, and HOSEPIAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 282) found that there was a slight increase in perfusion resistance in the hindquarters, reducing the rate of perfusion flow about 5 per cent, but no edema; that an increased perfusion resistance occurred in the intestines, reducing the perfusion flow about 25 per cent, with increased peristaltic movements, distinct edema of intestinal wall and increased

volume of intestinal contents; that a similar perfusion resistance and edema occurred in the liver, while a still greater perfusion resistance, reducing the perfusion flow fully 75 per cent, with marked pulmonary edema, occurred in the lungs. These reactions in intestines, liver and lungs were qualitatively similar to the histamine reactions previously reported, the hindquarter reactions differing in the absence of marked edema and in the substitution of a slight vasoconstriction for the marked histamine vasodilation. The authors call attention to the fact that "if reactions similar to those observed on blood-free perfusion of isolated organs take place during anaphylactic shock in the intact animal, one can readily understand why the acute fall in arterial blood-pressure, the characteristic feature of canine anaphylaxis, does not take place in dehepatized dogs. Peripheral vasoconstriction (intestines and hindquarters) would tend to increase the arterial blood-pressure in these animals, while the reduced blood volume from edema would tend to decrease this pressure."

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**An Anaërobe from the Mouth Cavity of Man and Rabbits Morphologically Suggesting *B. Pneumosintes*.**—In 1919, HOLMAN reported the isolation of a minute anaërobe out of material from the mouth of five consecutive persons not suffering from influenza. The material was cultured on cooked meat and other media and the organism attracted attention because of the abundance of gas it produced in the cooked meat, but more especially on account of its small size and the chance of its being confused in direct smears and mixed cultures with *B. influenzae*. More recently, HOLMAN and KROCK (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 280) reported the isolation of an anaërobic bacillus from the oral cavity of four of the workers in their laboratory—an organism which they consider as identical with the five strains encountered in 1919, and with another found in an infected neck and described in 1922. The anaërobe was very small, well under 0.5 micra long, by a little less in width, being smaller than *B. prodigiosus*, *B. bronchosepticus* and *B. influenzae* and about the size of *B. pneumosintes*. The coccoid bacillus was non-motile, Gram-negative, occurred singly, often in pairs, and in irregular groups, depending upon the medium, and was strictly and persistently anaërobic. Gas production in cooked meat medium was constant and copious and was the outstanding test tube biological feature. The bacterium passed through a Mandler filter tested against *B. pyocyaneus* but which allowed *B. prodigiosus* go through under 20 pounds' pressure. The authors consider this bacterium of importance because it may be confused easily with *B. pneumosintes* by its morphological appearance and its manner of growth, because it is filterable through tested filters, and because it is found in the oral cavities of man and rabbits and thus could lead to confusion with *B. pneumosintes* from these sources. The authors further indicate that "comparable experiments to those done by Olitsky and Gates will have to be carried out to determine whether this common extremely small anaërobe will alter the blood picture after intratracheal injection, or lower the resistance of the lung to secondary invasions by other common organisms of the respiratory tract, or will show any serological or other relationship to *B. pneumosintes*."

## HYGIENE AND PUBLIC HEALTH

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**Botulism. Studies on the Manner in Which the Toxin of Clostridium Botulinum Acts upon the Body. I. The Effect upon the Autonomic Nervous System.**—DICKSON and SHEVKY (*Jour. Exper. Med.*, 1923, 37, 711) believe that in botulinus intoxication in cats, dogs and rabbits there is a specific effect upon the portions of the autonomic nervous system which results in a blocking of the nerve impulses of these nerves. The experimental as well as the clinical evidence indicates that there is no damage to the nerves of the thoracicolumbar outflow. The authors state that the exact location of the damage has not been ascertained nor has the mechanism by which the nerve impulse is blocked been determined. The experiments show, however, that the lesions in these portions of the nervous system are not of central distribution but are peripheral, and the block cannot be due to an organic break in the conduction apparatus but must be due to some derangement which is relatively unstable. If it were otherwise it would not be possible to induce a physiological response even by massive stimulation, nor could the response be subsequently repeated by stimuli which lie within the limits of normal intensity. The application of the results of the experiments to the clinical manifestations of botulism will be discussed in a later report after the effect of the toxin upon the skeletal motor nerves has been described.

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**Experimental Observations on the Prophylaxis and Treatment of Syphilis.**—NICHOLS and WALKER (*Jour. Exper. Med.*, 1923, 37, 525) state that by inoculating the scarified surface of both sides of the scrotum of rabbits with suspensions of *Treponema pallidum*, 100 per cent of infections were obtained on one side or the other. Infection through the unbroken skin could not be produced. By gland transfers from animals with positive local inoculations, 87.5 per cent of takes were produced. These two methods were used to test the prophylactic value of 30 per cent calomel ointment. (a) Calomel ointment proved efficacious up to eight hours after inoculation with syphilis. (b) No marked difference appeared between the action of calomel in a base of lanolin and vaseline and in a base of benzoinated lard and wax. (c) Death from mercurial poisoning was produced in rabbits by a single application of a large amount of calomel ointment. The method of gland transfers was used to test the sterilizing effect of arsphenamine and neoarsphenamine on old infections in the rabbit. The infection was

completely abolished in every instance, whether by one, two or four intravenous doses. Natural spirochetosis of rabbits need not be a serious complicating factor in work on syphilis in rabbits, for the following reasons: (a) In natural spirochetosis, the lesions occur on the penis and not on the scrotum. Gland transfers are negative. (b) A scrotal lesion can be produced by inoculation, but it can be distinguished from that of *Treponema pallidum* infection by its course. (c) In studies of generalized syphilis supposed to involve the genitalia, and in sexual transmission experiments, *Treponema cuniculi* may be a serious complicating factor.

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**Obesity: Observations on One Thousand Cases.**—PREBLE (*Boston Med. and Surg. Jour.*, 1923, 188, 617) states that obesity is almost invariably due to bad dietary habits and not to errors in metabolism or to heredity. Overweight of 15 or more pounds is an increasingly serious condition with advancing years, conducive to heart, arterial and kidney disease, diabetes, and hypertension. Obesity is easily curable, and it is the duty of the physician to acquaint his patient and the community with the gravity of the condition and the ease with which it can be controlled.

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**Dengue Fever. A Clinical Report of the Galveston Epidemic of 1922.**—RICE (*Am. Jour. Trop. Med.*, 1923, 31, 73) states that the 1922 epidemic of dengue in Galveston followed a plague of yellow fever mosquitoes, and subsequently spread throughout the State. The disease presented a few characteristic features and should not be confused with other clinical entities. The rash may vary, but is distinctive. Uterine hemorrhages are common in dengue, and hemorrhages from any mucous surface may occur. Recurrences are seen, and partial immunity is of short duration, probably less than four months. The incubation period varies between four and fourteen days. Pregnancy is not disturbed. No specific treatment is known.

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**Weil-Felix Reaction in Rocky Mountain Spotted Fever.**—KELLY (*Jour. Infect. Dis.*, 1923, 32, 223) states that while the series of tests carried out by him is not large enough to warrant any definite conclusions, it suggests that the Weil-Felix reaction is negative in Rocky Mountain spotted fever and may be of value in differentiating between this disease and typhus fever.

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**Experimental Abortion in a Cow Produced by Inoculation with *Bacterium Melitensis*.**—EVANS (*Public Health Reports*, 1923, 38, 825) points out that *Bact. abortus* and *Bact. melitensis* are practically identical and that she has been able to cause abortion in a heifer with the latter organism.

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**A Report on the Indigent Migratory Consumptive in Certain Cities of the Southwest.**—WHITNEY (*Public Health Reports*, 1923, 38, 587) gives the results of an extensive study of the situation with respect to non-resident tuberculous cases in the southwestern part of the United States. It is shown that the large number of dependent or partially dependent consumptives who go to that part of the country generally

regarded as most favorable for the cure of the disease constitutes a serious financial burden on the communities to which they go. The facilities for caring for this class of cases referred to are wholly inadequate, though praiseworthy efforts are being made in many places.

**The Distribution of Malaria in the United States as Indicated by Mortality Reports.**—MAXCY (*Public Health Reports*, 1923, 38, 1125) makes a careful study of the data available on his subject, and gives the following summary: "This study of mortality rates from malaria indicates that the disease is largely confined to the Coastal Plain, reaching its widest distribution in the lower Mississippi Valley. The distribution of the disease is not uniform but focal in character. Areas of high prevalence are found chiefly about the mouths of large rivers along the coast, particularly in the 'delta' lands of the Mississippi and along the valleys of its large tributaries. In Arkansas, Louisiana, Mississippi and Florida a large proportion of the total land area and population is affected by the malaria problem. In the other States in the South the problem is more or less limited to certain sections of each State, the remainder of the State being relatively or entirely free from the disease. While there has been a general decrease in incidence of the disease in the past few years, this does not hold for all parts of the country. Mortality records indicate a definite increase in incidence for the Mississippi Valley during the year 1921."

**Studies on the Bio-assay of Pituitary Extracts.**—SMITH and McCLOSKEY (*Public Health Reports*, 1923, 38, 493-512) discuss the attempts which have been made heretofore to standardize pituitary extracts and show the lack of success which has attended the efforts. The great variation in commercial preparations is shown by their own work as well as by a study of the reports of others. A method of preparing a relatively stable extract in powder form is given, together with directions for carrying out comparative tests. Several factors which might improve the activity of infundibular extract were studied, as season, sex and freezing; all of these were without serious influence. Autoclaving is destructive of the activity of the material, but fractional sterilization of acidulated extracts is harmless.

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ORIGINAL ARTICLES.

OBSERVATIONS UPON THE NATURE, DIAGNOSIS AND CLINICAL  
MANAGEMENT OF GASTRIC ULCER WITH SUGGES-  
TIONS FOR A RATIONAL REGIMEN OF  
TREATMENT.\*

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**Introduction.** It requires but a casual acquaintance with the literature of peptic ulcer to demonstrate that treatment of the affection has been largely empirical. Various types of therapy appear to have obtained a vogue because their application relieved symptoms or for a time appeared to delay a fatal outcome. Success of modes of treatment has been judged from its effect upon the immediate condition and not with respect to the ultimate course of the ailment. Statistics of hospitals or private practices rarely indicate the condition, digestively, of patients treated after five to twenty-five-year intervals following a particular mode of therapy. As a rule, hospital records state that a peptic-ulcer patient has been discharged "cured," "improved," "not improved," or has "died." With exception of the fatal cases, usually facts are not available regarding the future course of the disease, inasmuch as patients frequently seek the advice of another physician, should their disability return after a long and expensive course of treatment at the hands of one physician. It is also of interest to observe that of a half dozen *experts* non-surgically treating peptic ulcer by radically different regimens, the percentages of *cure* show a variation of but five to ten points. I have also been impressed by the

\* Oration in Medicine, Virginia State Medical Association, Norfolk, Va., November 1, 1922.



fact that at the most competent hands, certain ulcers alike resisted all types of treatment. It has seemed to me that unsatisfactory as the treatment of peptic ulcer might be, it should be possible to devise a type of management that at least had the merit of resting upon certain basic principles. It likewise appears to me that methods of therapy should be based upon information that has been returned by modern histological, physiological and clinical investigation. All too frequently the mind, medical, has confused *kur* (a form of clinical management) with *cure*, the actual eradication or substantial healing of a pathological lesion.

**The Nature of the Problem.** The problem is not a simple one, even though for some eighty years attempts have been made by numerous clinicians to have it appear as such. Those observers who, either by pathological, chemical or clinical training, are most competent to speak, admit that facts are not yet at hand which really permit our making unqualified statements with regard to either the cause, course or cure of the ailment.

Clinically, peptic ulcer is a disease which may or may not exhibit symptoms or signs. It is an ailment which, in its uncomplicated form, may be so closely mimicked clinically by non-ulcerous dyspepsias as to deceive the most experienced diagnostician. Until complications occur, it is a disease characterized in 84 per cent of instances by a peculiar *periodicity*. It frequently manifests itself by recovery and relapse wholly independent of type or duration of treatment. It is associated with a form of gastric malfunction, the cessation of which does not necessarily indicate eradication of its exciting causes. It is a disease about which little prophecy respecting its extent or its future course can be made from its clinical symptomatology. Acuteness of symptoms does not wholly indicate the histopathological changes existing at the diseased focus; acute manifestations, histologically, can complicate chronic inflammatory lesions pathologically. The most serious clinical outcome may follow upon *spontaneous* or so-called *therapeutic* cure, accompanied by the subsidence of the initial dyspeptic upset. Stenosis, gastric malformation, involvement of extragastric viscera, fatal hemorrhage, or malignant transformation may occur with comparatively slight clinical manifestations or certainly with relatively little change in the patient's complaints. Peptic ulcer is an ailment indistinguishable, clinically, from the appearance of beginning gastric cancer, or gastric involvement by syphilis, or tuberculosis. It is a disease which but rarely occurs in individuals not already affected with other clinical abnormalities, as infections about the head, throat and neck, abdominal diseases, *i. e.*, inflammatory changes in the appendix, gall-bladder, perigastric lymph nodes, pelvic structures; disturbances in the circulatory, eliminative, nervous or lymphatic symptoms or malfunctions of that group of glands concerned with food digestion and assimilation. Finally,

it is an ailment of almost universal distribution, and one capable of producing such disturbances of the physical and mental health, as to demand relief.

**Etiology.** A study of the affection demonstrates that a narrow conception of the etiology of peptic ulcer is quite erroneous. Competent observers have experimentally produced gastric ulcer by a wide variety of methods. It has been shown that gastric ulcers differing slightly in type, histologically, can be caused more readily from the systemic than from the local intragastric point of attack. Some of the more familiar causative agents are: (a) Bacteria of various types and strains, the evidence apparently indicating that any organism capable of multiplying in the blood and lymph streams and being viably implanted in the stomach's or duodenal's wall may furnish the beginning of ulcers; (b) bacterial toxins; (c) cutaneous burns; (d) elements of metabolic origin (Bolton's "gastrotoxin" injected intraperitoneally or subcutaneously); (e) metallic and alkaloidal poisons; (f) poisons introduced directly into the stomach (corrosives, caustics); (g) alterations in the stomach's circulation (vascular blocking, adrenalectomy, thrombi, emboli, arteriosclerosis or nervous imbalance, external pressure); (h) artificial pyloric spasm or stenoses; (i) mechanical trauma and food or foreign protein intoxications. But whatever may be the experimental mode of production, the ulcers resulting differ slightly. The lesions produced which are essentially similar from all causes are: Local inflammatory edema, loss of surface epithelium, minute or gross hemorrhage, necrosis, glandular destruction and frequently secondary infection. In the healing of ulcers, irrespective of the way that they may have been produced, the basic features consist in development of protective connective tissue by hyperplasia with resultant scar. Ulcers in which the underlying causative agents persist constantly or become intermittently active heal the most slowly. It is by such incomplete attempts at repair that, from so-called *acute* beginnings, pathological chronicity is induced. Recently I have summarized, clinically, what appeared to be etiological factors associated with 522 proved, histologically, chronic gastric ulcers:

TABLE I.

Group.	No. of cases.	Per cent.
1. Infections (chronic and acute) . . . . .	173	33.7
2. Arteriosclerosis (with vascular hypertension, 56 cases; without vascular hypertension, 21 cases) . . . . .	77	14.7
3. Visceral hypertonia (vagus or splanchnic hyperfunction) . . . . .	68	13.0
4. Chronic general anemia (so-called "chlorotic") . . . . .	61	11.3
5. Syphilis . . . . .	41	7.8
6. Visceral hypotonia (vagus or splanchnic hypofunction) . . . . .	27	5.2
7. Postoperative . . . . .	27	5.2
8. Industrial intoxication (occupational poisonings) . . . . .	22	4.2
9. Metabolic dysfunction (thyroid, suprarenal, pituitary, etc.) . . . . .	18	3.4
10. Trauma (abdominal injury from blows, falls, etc.; intragastri- cally, foreign bodies) . . . . .	8	1.5

To the seriously inclined student of peptic ulcer and its clinical management, the classifications given will prove of a certain suggestive value and furnishes significant hints respecting the possibilities of the various so-called *curative* regimens. It is quite likely that similar constitutional disturbances are associated with duodenal ulcer.

The summary given indicates that, with the evidence at hand, one cannot expect to establish a single definite cause of peptic ulcer. Seemingly, the exciting and localizing causes of ulcers vary widely and are individual for each subject. The essential point is that, through some systemic, and later local gastric malfunction, a point of least resistance occurs in the mucous membrane and normal gastric physiology is permitted to produce an *abnormal* tissue change. It would likewise appear that we have no basis for regarding peptic ulcer as a distinct disease entity. It seems *more proper to consider that ulceration of the gastric mucosa is a local accident in the course of a systemic upset, the nature of which upset may be extremely varied.* When once damage has been done locally to the wall of the viscus, whatever may be the primary cause, the future course of the process is similar. Pepsin and hydrochloric acid attack the inert gastric cells, necrosis results and ulcer is established. The course, duration and complications of the process depend mainly upon the persistence of the underlying systemic causes, variation in the quality of the gastric juice, local intragastric trauma (as by food, bacteria, etc.) and the influence of the activity of the muscles forming the stomach wall. *Such facts strongly suggest that peptic ulcer presents many aspects of a self-limited ailment.* The role of the physician lies chiefly in the management of the acute or chronic accidents and complications consequent upon the destructive action of the primary cause interacting with the capacity of tissue to protect and repair itself.

From the inception of symptoms, it is impossible to predict clinically the future course of any peptic ulcer. While many ulcers associated with a transiently acting causative agent destroy relatively little gastric mucosa and produce harmless scarification, thus evidencing a tendency to spontaneous cure, other ulcers, seemingly equally innocuous clinically at first, progress rapidly through various pathological stages and in a short time are associated with stenosis, extensive callous formation, hemorrhage, perforation or malignancy. Chronicity in the histo-pathological sense by no means indicates that a peptic ulcer is old in terms of months or years. Malignant changes in gastric ulcer edges may occur quickly and their presence in no way points to the long existence of a previously benign affection.

It is significant to observe variation in the pathological type of ulcers, dependent on their situation in various parts of the stomach. While fully 85 per cent of all gastric ulcers occur in the pylorus,

antrum, and along the distal four-fifths of the lesser curvature, and while in these positions the greatest damage can be done by ulcer, yet just as striking changes occur in ulcers situated in other portions of the viscera. It is of importance to note that fully two-thirds of the gastric ulcers occur in that portion of the stomach, the mucous membrane of which is not devoted to the elaboration and secretion of hydrochloric acid, and that duodenal ulcers lie in a mucosa devoted to secreting an alkaline juice, but subjected to vigorous motion and to traumata, physical and chemical, from chyme. It would also seem to be of significance to recall that the majority of peptic ulcers occur in that part of the gut in which the greatest circulatory, muscular and neurological activity is requisite, that the fewest ulcers occur in those parts which are relatively fixed, and which have to perform mainly the duties of food receptacles or of a pepsin-secreting tubular gland.

**Physiology.** (a) *Gastric Chemistry.* It is a striking commentary upon the empirical nature of standard treatments of peptic ulcer that they have as their basis the principle that gastric chemistry has been previously upset. It has been supposed that this disarrangement has been caused either by the development of ulcer or that the upset itself has produced the ulcer. This chemical disturbance is generally put down as being in the nature of an overproduction of acid gastric juice and pepsin. It is presumed that the so-called "corrosive effects" of this overactive digestive juice produces gastric ulcer or prevents healing of one already present. It is significant to observe in the first place that the normal gastric juice frequently varies in strength well beyond the range of the so-called increases, which may be demonstrated when gastric ulcer exists. In a recent study of 500 cases of gastric ulcer in but 30 per cent did I find free HCl values above 0.25 per cent. In 45 per cent the acidity was well within the normal range, and in the remaining 25 per cent the acidity was reduced or was entirely absent. Similar observations have been recorded by other clinicians. That there are causes of gastric ulcer other than the variation in the hydrochloric-acid concentrations is also supported by the observation that in bile-free stomachs large amounts of hydrochloric acid in the concentration of higher than 0.6 per cent mixed with pepsin may be placed in the stomach and yet not produce ulcer. Clinical and histo-pathological evidence indicate that when once initial damage to the gastric lining has been brought about, from no matter what cause, digestion of partly devitalized or necrotic mucous membrane may occur with equal readiness in the presence of normal or even subnormal gastric acidity. Whenever there exists the triad—dead protein, hydrochloric acid, pepsin—the process of local, tissue digestion may go on. It is also quite likely that frequently HCl and pepsin may be absent and destruction of devitalized gastric or duodenal mucosa follow from the

eruptic activity of bacteria in the wall of the gut (primarily or secondarily implanted there systemically or from the lumen of the viscus) or from erepsins present in reflux pancreatic juice.

With these facts in mind it seems strange that treatment of gastric ulcer has largely rested upon a chemical foundation, which chemical foundation is unstable and shifting. Without responsible scientific data, it has been presumed that in ulcer stomachs overacidity was present, and that this overacidity must be counteracted by alkalization before healing could take place. It has been presumed that the pain of gastric ulcer existed as a consequence of irritation and corrosion of raw mucous surfaces, by gastric juice rich in hydrochloric acid and pepsin, even though the researches of Pawlow, Rehfuß, Carlson, Hertz, Hamburger and others have demonstrated that pain is not commonly present when gastric acidity is highest and that, in known ulcer cases, the introduction of high percentages of acid fails to produce pain. The relief from pain in gastric-ulcer cases is quite as prompt when alkalies are administered in low acid cases, as when such are used in high acid cases. Prompt relief of pain in such instances is also secured by the exhibition of non-alkaline agents, *e. g.*, lavage, antispasmodics, alcohol, opiates, diet, etc. It would seem, therefore, that treatment of peptic ulcer based upon chemical upsets supposed to be associated with the ailment presents much that is empirical and without scientific foundation.

(b) *Gastric Motility.* Modern physiological investigations have been especially rich in elucidating the motor activity of the stomach under normal and pathological conditions. Investigators have established the significance of certain gastric cycles of motor activity. They have shown that normally these cycles occur with almost mathematical precision. It would seem that the mechanical factors concerned with digestion are of greater importance than are variations in the secretory function.

The fasting stomach is in a state of tonic contraction. It is rarely empty. Its contents consist of both hydrochloric acid and pepsin. These secretions aid in preserving gastric tone, in digesting mucus, dead bacteria and desquamated cell detritus. Normal hunger is manifested by rhythmic gastric contractions. These seem to precede appetite desire and cause a "want" that leads to eating. Repeated swallowing motions cause certain inhibitions of gastric tonus. Eating accelerates gastric-juice secretion and rhythmic gastric contractions. These peristaltic movements continue so long as food remains in the stomach. They pass from the *pars media* toward the pylorus in regular sequence, thus maintaining a constant pressure in the antrum. Abnormal increases in intragastric tension are prevented by variation in the rate and intensity of the peristaltic contractions and by the rhythmic, interdependent systoles and diastoles of the cardiac and the pyloric

sphincters. The proximal third of the stomach acts mainly as a sac or reservoir and is comparatively free from peristaltic activity. The discharge of chyme from the stomach is intermittent. Seemingly, the pylorus is in some way dependent upon variations in intragastric tension coupled with gastric acid concentration. The presence of acid chyme in the alkaline duodenum may have an influence upon the movements of the pylorus. Acid chyme stimulates the flow of pancreatic juice and bile. It has been advanced that the period of time necessary for these alkaline fluids to neutralize the acid chyme delivered to their reservoir of flow (duodenum) had a local influence with respect determining the duration of pyloric sphincter systole. However, this observation, first made by W. Cannon, has not been fully verified. The alternate opening and shutting of the pylorus with discharge of chyme is continued until the stomach is empty.

(c) *Influence of the Kind of Food Ingested upon Gastric Secretion and Gastric Emptying Time.* Water and normal salt solution cause limited gastric secretion and rapid stomach emptying. Their exit arouses but feeble peristalsis. Carbohydrate foods leave the stomach quickly on account of their failure to unite with acid gastric juice. Marked retardation in the discharge of carbohydrates, however, occurs if such be mixed with *alkaline* solutions. The alkali delays the normal feeding-acidity of the stomach and probably permits prolongation of salivary digestion in the stomach. What effect such introduction of an abnormal chemic reaction into the stomach chamber has upon gastric peristalsis has not been explained. Protein food leaves the stomach more slowly than do carbohydrates because proteins combine with free HCl, secondary digestion products develop, and if protein be fed in excess seemingly gastric motor activity is outweighed by the excess secretory activity demanded. Protein has also been shown by Khingine to cause the secretion of 50 per cent more gastric juice during the first four hours of digestion than when carbohydrate is fed. The *pyloric spasm* resulting may then not be in the nature of a true spasm, but merely the evidences of an abnormally prolonged, but not necessarily intense pyloric systole. However, such prolonged systole of the pyloric sphincter may be responsible for a pathological increase in intragastric tension; not infrequently an accompaniment of this is regurgitation of gastric contents into the esophagus, whose cardiac sphincter has been thrown out of normal rhythm by the prolonged pyloric closure. Clinically, this is manifested as "water brash," "sour stomach," pyrosis or even vomiting. Cannon states that at the end of a half hour eight times as much carbohydrate as protein has passed from the normal stomach and that there exists twice as much carbohydrate as protein in the jejunum. While normally carbohydrates begin to leave the stomach at once after feeding, proteins remain from one to three

hours. Fats tarry longest in the stomach; they excite little free HCl productions and excess fat feeding appears likewise to arouse but feeble gastric peristalsis.

Vigorous mixing of food with acid chyme occurs in the antrum and the pylorus, the zone in which 60 per cent of all gastric ulcers are found. Food delay in this locality permits of increased local movement of the viscus, greater opportunity for food and acid to remain in intimate contact with injured gastric lining: hence, opportunity for the maximum of trauma, infection, digestion of damaged tissue, stress on the pyloric sphincter and local alterations in circulatory and neuromuscular mechanism.

The facts enumerated above would appear to have been established as constants by repeated laboratory and clinical investigation. In my opinion they furnish a logical ground-work for the treatment of peptic ulcer. At least, as these observations place such treatment upon the only rational basis which we at present know of; their application is an attempt to eliminate many purely empirical and "rule-of-thumb" features, such as characterize commonly accepted modes of therapy. I am convinced of the practicability and usefulness of their clinical application after eleven years of careful observation.

**Diagnosis.** In order to insure anything like satisfactory results from measures directed toward the relief or cure of peptic ulcer, it is quite necessary that, before special forms of treatment are instituted, one should have definite proof that ulcer actually exists. This may seem a very trite truism, but is fully warranted and cannot be stated too frequently or too emphatically. In going about the country and mingling with men engaged in hospital or in private practice, I am quite ready to agree with Deaver, who states that not one-half of the patients who are being non-surgically treated for ulcer of the stomach actually have such ulcer, and with W. J. Mayo, who, in opening a discussion on the surgical treatment of ulcer some years ago in the late John B. Murphy's Clinic, began with the statement, "First catch your ulcer." Mistakes in diagnosis of peptic ulcer occur most frequently in clinics or practices where the diagnosis depends chiefly upon history and physical examinations made in accordance with principles laid down by authors who wrote text-books sixty to seventy years ago, or by those modern parrot-scribes who have revamped the old material and turned it loose without experienced scrutiny.

Fully 5 per cent of peptic ulcers give rise to no symptomatology whatever. These ulcers are happened upon during abdominal exploration at laparotomy. In fact, peptic ulcer clinically does not of itself give rise to characteristic symptoms and signs, unless it is associated with such accidents or complications as protected or unprotected perforation, gross hemorrhage, pyloric or cardiac obstruction, etc. Such clinical symptoms as are commonly asso-

ciated with the presence of peptic ulcer to the general medical mind, namely, epigastric pain or distress, pain occurring at the height or after the height of digestion (which pain is usually relieved by taking food), "water brash," pyrosis, so-called sour stomach, heartburn, nausea or vomiting, are but happenings dependent upon certain motor disturbances in gastric physiology. Briefly, these clinical symptoms follow anything which produces local or general gastric spasms accompanied by increased intragastric tension. It thus follows that the symptomatology of peptic ulcer is common to such other abdominal ailments as may produce disturbances in gastric motility. Consequently, many individuals who are affected with chronic appendicitis, chronic infections of the biliary tract, inflammatory lesions of the bowel or of the gastric walls, may experience the clinical syndrome above mentioned. The reason why any so-called diagnostic clinical symptomatology can be attached to real peptic ulcer is that peptic ulcer histologically is in the great majority of instances an intermittently active pathological process. It follows, then, that, in the periods of activity, patients exhibit symptoms dependent upon pyloric and gastric spasms with increased intragastric tension, but that the spontaneous or other type of healing of the ulcer is succeeded by a symptom-free interval when the gastric motor function returns to normal. In the attacks, the gastric motor-spasm syndrome and its associated symptomatology are quite similar in kind to a similar motor-spasm syndrome produced by pathological lesions outside of the duodenum and the stomach (particularly those located in the biliary tract and appendix zones), but with ulcer the symptoms are quite likely to be of aggravated degree. The "gastric motor-spasm syndrome" initiated by extra-duodenal or extragastric lesions is not likely to be so characteristically intermittent in its course as is that associated with peptic ulcer. This, itself, is of great diagnostic importance. In fact, to the experienced the chief lesson learned from taking a careful history from patients suspected of peptic ulcer is that of discovering an ailment giving rise to intense disturbance in gastric function at intervals—not as a rule continuously—and that, between these "attacks" the patient is well and happy. If one definitely proves this in the anemnesis he has attained the most valuable single diagnostic fact possible to secure from the history.

Pseudoulcerous dyspepsias commonly occur in young adults affected with biliary-tract or appendix disease. Such ailments are rarely associated in the young with true peptic ulcer, but are very commonly indeed diagnosed as peptic ulcer and treated as peptic ulcer over long periods of time. They furnish that great mass of so-called "acute" or "non-deforming" peptic ulcers, found in the majority of clinics where non-surgical treatments are in vogue or where any widely preached procedure is considered a special feature of such clinics.



True peptic ulcer has proved, in our experience, to be uncommon in individuals of either sex below the age of thirty. The gastric motor-spasm syndrome, so commonly mistaken for ulcer in these young adults, is dependent upon lesions of the appendix zone or the biliary tract in 80 out of 100 patients where it is manifested. This we have proved by carefully following through 2200 patients with the gastric motor-spasm syndrome and below the age of thirty years. We have been so seriously impressed with the significance of our observations and with the folly of attempted non-surgical relief of this type of dyspepsia in the young, that, in individuals under the age of thirty years, who exhibit what the text-books call "acute" ulcer symptoms, unless these symptoms have been accompanied by gross hemorrhage or by perforative gastric or duodenal signs, we have refused to make an unqualified diagnosis of peptic ulcer. This is an important observation, when it is remembered that the group about which we are speaking furnishes the great bulk of "ulcers" being non-surgically treated in the various special clinics or in general practice.

The *abdominal examination* in a peptic ulcer uncomplicated by gastric obstruction or deformity or by perforation returns no significant information. Many of the so-called characteristic local areas of epigastric tenderness are zones of muscle spasm due entirely to extragastric or extraduodenal disease. I am convinced that very frequently, indeed, when doctors point out characteristic areas of abdominal tenderness, such tenderness, as is elicited, is due to pressure upon the spinal nerve roots. Similar areas of tenderness can be readily demonstrated on the other side of the midline.

The *gastric test-meal* furnishes no pathognomonic information. We must get out of our heads and the text-books the idea that increase in gastric acidity means ulcer and that decrease in gastric acidity means that ulcer is healed or is absent. There are too many variations in the normal degree and rate of secretion of gastric juice ever to permit the statement that in any individual the finding of high HCl values is due to or indicative of ulcer.

Our records show that approximately 30 per cent of proved ulcer cases were associated with what might be termed increase in hydrochloric acid values; that the majority of patients had acid within the so-called normal range, while 25 per cent had no free HCl acid or the acid secretion was very low; yet, with all these variations in acidity, in the great group of patients there was no associated variation in clinical symptomatology or in the rate of ulcer progression or of healing.

*Test-meal Blood—Occult or Gross.* Similarly, the finding of blood in a gastric test-meal or the failure to find it does not mean that ulcer exists or that ulcer is absent. If there is a large ulcer accompanied by much epithelial erosion, then the finding of blood

indicates that an ulcer which is present is, at that particular time of examination, active. Thus, one can appreciate the significance of our own records: Gross or occult blood was present in rather less than 40 per cent of gastric contents and detected in about 33 per cent of the stools. We have never found that such tests as the Einhorn string test and other clinical playthings proved in any way useful in accurately detecting the presence of or of locating peptic ulcer. Many of the blood stains upon these swallowed strings undoubtedly result from the wet string cutting the mucous membrane of the stomach at points of constriction and do not indicate real peptic ulcer. In more than 300 "string" observations upon proved ulcers we had a scant dozen blood stains which might have been liberally interpreted as points of contact with the bleeding ulcer surfaces.

*The capacity for gastric emptying* is not infrequently interfered with where ulcers occur near the pylorus, either on the gastric or the duodenal side. If a patient takes a full dinner and *persistently* has retention in his stomach upon lavage eight to twelve hours following the ingestion of that dinner, then it may be considered that there is a mechanical defect—a definite reason why the stomach cannot have its contents negotiate the narrowed passageway. In chronic ulcer more than 41 per cent of patients with gastric ulcer exhibit persistent eight to twelve-hour retention, and more than 60 per cent of duodenal ulcer exhibit a similar retention. In 1911, I published these facts, and also showed how important it is in suspected ulcer patients to examine the fasting stomach eight to twelve hours after the administration of a full dinner. Since then emphasis upon this procedure has been made by Straus and Hansman and very recently by Gaither, of Baltimore. I consider that the information derived from thus testing the emptying power of the stomach under the stimulus of a full meal furnishes the chief excuse for giving patients test-meals at all.

The *roentgen-ray* has been of great service in aiding us to recognize whether ulcers are in the stomach or in the duodenum and to give us an idea with respect to the degree of damage which real ulcers have brought about in the gastric and duodenal walls and to adjacent viscera. The roentgen-ray has also led to a complete revision of our statistics as to where peptic ulcers occur and to the relative frequency of incidence of ulcers in the duodenum and in the stomach. Certainly, practically all of our statistics on this point, gathered and published previous to twelve years ago, are valueless and should be consigned to the waste-basket. The roentgen-ray has enabled us to show preoperatively about 50 per cent of true gastric ulcers and between 60 and 70 per cent of duodenal ulcers. I am quite aware that higher percentages are claimed by some roentgenologists, but when one checks up their reports he is quite apt to find that diagnoses unqualified by "prob-

able" or "possible" ulcer rarely reach higher than the above figures. The roentgen-ray is our most useful single diagnostic agent, not only in the recognition of ulcer but also for determining the damage which ulcer has produced. It is our custom to lay great emphasis upon the roentgen-ray showing evidences of gastric deformity, official obstruction, displacement and fixation of organs and the like. We consider that when the roentgen-ray shows persistent, local, gastric or duodenal malformation there is little hope of the patient receiving permanent benefit from non-surgical therapeutic procedures. This is so because not only have we then to deal with a lesion which, if it be in the stomach, is a potential cancer, a lesion which may be complicated even when the patient is symptom-free by fatal hemorrhage or perforation, but because scar tissue production deforms the stomach and seriously interferes with emptying time and normal secretory function.

**Treatment.** Keeping in mind the conception that peptic ulcer is rarely a primary gastric or duodenal fault, but is usually a secondary happening in the course of an acute systemic or chronic constitutional disturbances, it becomes evident that if one is to rationally attempt relief or cure of peptic ulcer he must recognize the primary etiological fault and attempt its eradication or its alleviation. It follows then that one must as energetically treat the patient who harbors the ulcer as he does the ulcer in that patient. If this be the plan of action, provided one has not to deal with such acute accidents as hemorrhage or perforation or such chronic complications as stenosis, visceral deformity and fixation, malignant degeneration, etc., the peptic ulcer will heal after Nature's fashion if too much interfering effort is not applied, intragastrically and intraduodenally.

(a) SELECTION OF CASES FOR TYPES OF TREATMENT. As I have said, recognition of the primary systemic fault is often difficult. Inasmuch as foci of infection may exist in oral adenoid tissue, head sinuses, about teeth or in systemic lymph-gland chains, these must be removed promptly. Intra-abdominal infections must likewise be eradicated, *e. g.*, diseased appendix, gall-bladder, Fallopian tubes, ovaries, ulcers or subinfections of the bowel. It would appear quite inadequate to remove external, local foci of infection and to leave behind intra-abdominal foci containing bacteria already accustomed to their environment and ready to spread their operations to the gastric or duodenal lining when opportunity offers. It would appear that the removal of these variously situated germ centers constitutes a fundamental step toward the cure of many gastric ulcers. Careful general scrutiny of the patient for cardiac leakages, myocardial insufficiency, capillary sclerosis, anemia, evidence of occupational poisoning, endocrine malfunction, improper environment, overwork or nervous stress must be made. These are all causes leading to or aggravat-

ing ulcers. If their importance is minimized, then advantage of aid from the constitutional side of the individual is lost and ulcer healing certainly delayed. At least two negative Wassermann tests should be recorded before any treatment which excludes antiluetic therapy is decided upon. It is quite surprising how frequently a positive Wassermann test, even though a history of lues cannot be obtained, will aid in the exhibition of remedies and accelerate ulcer *cure*.

After local foci of infection have been removed the mode of treatment is further influenced by the type of ulcer that has been proved to exist. Unless ulcers complicated by much scarring or causing great gastric deformity are demonstrated to be luetic, little hope of permanent relief by medical regimens can be offered. Surgery promises the greatest prospect of relief to such cases. Intense pain, frequent hemorrhage, perforation or the danger of malignant change taking place in calloused ulcers likewise contraindicate non-operative care. Unfortunately we have no clinical or laboratory tests which indicate to us what type of gastric ulcers will become malignant or when early malignant change is taking place. However, we can be consoled by knowing that malignancy in connection with duodenal ulcer is rare. The roentgen demonstration of calloused gastric ulcer exceeding 2 cm. diameter, when such is associated with history of frequently recurring ulcer symptoms and the positive chemical test for blood constantly determined in the stools, forms a clinical hint that malignancy can be expected. The most competent clinicians are agreed that calloused recurring ulcers located in the pyloric end of the stomach should be treated operatively. Excision should be performed when mechanically possible. If excision is impractical then infolding or cautery puncture, with or without gastrojejunostomy, yields the most satisfactory results. In non-obstructing ulcers it would seem that gastrojejunostomy should always be accompanied by permanent pyloric closure if one is to secure a perfect and permanently emptying stoma. Gastrojejunostomy, properly performed, acts by aiding gastric emptying, by decreasing intragastric tension, by, at least temporarily, diminishing free HCl (an average of 20.5 points in 273 consecutive cases in our series) and by permitting limited alkaline jejunal regurgitation into the stomach.

Thus, successful non-surgical treatment of ulcer first demands careful selection of cases to be so treated. It is indicated only in ulcers associated with little callus, or if calloused, located in portions of the stomach in which stenoses are not liable to result, or where surgical procedures cannot be carried out. Certain essential principles brought out by our review of the ulcer problem given above must be borne in mind in carrying out medical treatment.

(b) PRINCIPLES UNDERLYING TREATMENT. The most useful features of what I have suggested with respect to the non-surgical management of peptic ulcer are:

1. The recognition that such ulcer is not a primary gastric ailment; treating it as such without bearing in mind its systemic or constitutional origin offers little hope of permanent improvement.

2. Recognition of the type of ulcer at hand (from the etiological as well as the histological viewpoints) is absolutely essential before any method of therapy can be rationally directed.

3. Gastric chemistry plays a comparatively insignificant role both in ulcer production and in delay in ulcer healing. Ulcer dyspepsia is largely the manifestation of abnormal gastric spasms, disarrangement of normal gastric peristalsis and an excessively increased intragastric tension.

4. The principle underlying all local treatment of the gastric fault is the fundamental one of giving the injured part *physiological* rest and then not interfering with the natural tendency to heal inherent to all body tissue. *By adopting this principle of physiological rest to the affected part, it will be recognized that I have brought into the non-surgical therapeutic regimen of peptic ulcer those essential principles for healing which our surgical colleagues have so effectually proved necessary to the repair of any traumata whether by incision or from extraneous agents.* Whether the surgeon has to deal with an abdominal wall cut or a varicose ulcer of the leg, he finds that most rapid and permanent healing follows rest by fixation, suitable posture, favorable temperature, cleanliness and the avoidance of traumata from movement, antiseptics or so-called "healing" lotions, pastes and powders.

In actual practice physiological rest and repair of tissues harboring gastric ulcers are obtained in my clinic by the following regimen:

(c) OUTLINE OF A METHOD OF NON-SURGICAL MANAGEMENT.

1. *Rest in Bed.* Physical and mental rest for from one to three weeks; bodily and psychic activity alike are capable of stimulating peristalsis.

2. *Physiological Rest to the Affected Part (Stomach).* Complete rest demands avoidance of food, *per orem*, irritating medicine, gastric lavage and frequent abdominal examinations of the suspected focus.

3. *Local Applications to the Abdomen.* Painful spasms are prevented by having constantly applied to the abdomen compresses saturated with a hot solution of alcohol and boracic acid. These compresses may be kept heated by an electric pad or partly filled water bag and should be worn day and night without interruption.

4. *Keeping the Stomach Empty of Food.* This promotes healing by limiting local irritation from the food itself, by reducing the amount of gastric juice required to digest food, by limiting gastric peristalsis and by avoiding painful gastric spasms, which last tend to prevent free circulatory interchange at the ulcer-bearing area. Abstinence from food by mouth should be insisted upon for from

three to seven days, according to the type of patient under care. The period of fast is determined best by the clinical disappearance of gastric spasm (pain, regurgitation, "water brash," "heart-burn") and by fluoroscopical proof of absent or diminished gastric peristalsis. During the fasting period, paraffin wax is chewed for ten minutes every hour. The wax mechanically keeps the mouth clean, promotes free flow of protective saliva and mucus, prevents parotitis, aids in counteracting the development of painful hunger contractions and gastric spasm, local and general, and allays thirst.

5. *Rectal Feeding.* During the fasting period rectal feedings are instituted. From 300 to 600 calories of nutrient mixture are given each twenty-four hours in approximately 1000 cc of normal salt solution. I use a clyster containing 1 ounce of 50 per cent alcohol, 1 ounce of glucose, and normal salt solution to make 240 cc. The nutrient enema is given at body temperature by the drop method. The drops flow at the rate of 30 to 60 drops a minute and at least four such clysters are given in twenty-four hours. Should the patient be in great pain or affected with pronounced gastric irritability during the first day of rectal feeding, tincture of opium or tincture of belladonna (10 drops), or both, are given in each nutrient enema.

6. *Mouth Feeding.* When mouth feeding is begun (usually from the third to fifth day) two principles control the basis of diet: (1) Nourishment should be liquid and administered warm in small quantities, and these given frequently, and (2) carbohydrates should be selected.

(a) Small quantities of liquid food should be frequently administered in order that the stomach may empty rapidly, with the least effort on its part and thus it may remain food-free for the longest time. This procedure makes available the maximum time for rest at an ulcer site. Jejunal digestion must be called upon until gastric conditions warrant functional activity by the stomach. A fasting, food-free stomach contains hydrochloric acid or pepsin at a minimum. When the feeding *per os* is begun, from 2 to 4 ounces of warm liquid nourishment are given each waking hour. When gastric irritability is very pronounced and the patient is in great need of food, carbohydrate mixtures may be given intermittently or constantly with the aid of a duodenal tube, constantly *in situ*.

(b) As experimental facts have established, of all basic foods, carbohydrates leave the stomach most quickly and give rise to the minimum amount of functional activity. Therefore, liquid carbohydrate mixtures (barley water, rice gruel, thin cream of wheat, dextri-maltose, ovaltine, malted milk, thin creamed vegetable soup, etc.) are allowed. *Milk is not given as routine.* Milk results in almost pure protein clots in the stomach during its prepar-

atory stages of digestion. In the stomach these clots act precisely as do other proteins: they remain for a long time, act as sources of irritation, as stimuli to acid and pepsin secretion and furnish choice culture media for bacteria. If milk be given at all it should be first parboiled, citrated or predigested. If the gastric contents are low in acid and their bulk is carbohydrate, slight demands are *made upon the stomach as regards either secretory or motor activity*. The pylorus thus remains free from prolonged systoles and quick gastric emptying follows. By this means, the stomach avoids gastric stagnation and the intragastric accumulation of relatively high free and combined acids; particularly their accumulation in a viscus whose *tonus* or *tension* is apt to be greater than normal. This free gastric emptying prevents the development of hypernormal peristalsis, the influence of which factor is potent in the prevention of physiological rest (secretory and motor) to the ulcer area. It also renders unnecessary frequent, disturbing, gastric lavage or the exhibition of hugh quantities of alkaline drugs.

7. *Limitation of the Overproduction or Overaccumulation of Free Gastric Acid.* This is obtained by keeping the stomach food-free as above described. The ordinary stomach secretes very little HCl and pepsin after a forty-eight-hour fast; its peristaltic activity is held in abeyance or very feeble after this interval. The stomach is then in a state as ideal as possible for epithelialization at the ulcer site.

If the above points, as established by modern physiological research, are borne in mind, the exhibition of large quantities of alkali or other medicines is unnecessary. Many of our patients receive no medicines whatever by mouth. Pain, vomiting, regurgitation and pyrosis quickly disappear. Healing is accelerated and duration of hospital residence is shortened. Providing the gastric lumen is patent, the stomach empties freely; there is no stagnant, irritating residue requiring frequent lavage in order to insure the subject's comfort. Large quantities of alkali, according to Pawlow and to our clinical and laboratory experience, create pernicious increases of gastric acid and of mucus. Relief by lavage is then demanded. It would seem an absurd and contradictory clinical procedure to exhibit alkalies and thus create an intragastric state which then calls for removal of the accumulated foreign mass in order to insure a patient's comfort. It is true, that often large quantities of alkali bring about relief of symptoms, but mere symptomatic quiescence in no way indicates healing of gastric ulcer. The stomach has a remarkable capacity for neutralizing huge doses of alkali if it is compelled to do so, but there is no physiological reason why it should be called upon thus to overwork, when, physiologically, secretory activity may be controlled by fasting and later by diet. It will be remembered that the normal

habitat of gastric epithelium is an acid or, at the best, a neutral medium. If such epithelium is made to live in the presence of excess alkali, it lives under the handicap of an environment foreign to it constitutionally. Experiments in artificial tissue growth have shown that cell proliferation is retarded by hypertonic alkaline quite as well as by high acid solutions. Hence, overalkalinization may actually prevent healing. Attempts at protection from this foreign body (excess alkali) are shown: (1) By the acid-producing glands oversecreting; (2) by the mucoid degeneration of physiological fatigue, which results in the throwing out over the secretory glands of a protective layer of mucus; and (3) by delay in repair. Excess or continuous exhibition of alkali results in enormous secretion of acid and mucus; this is at least a partial explanation of the so-called "hypersecretion" associated with gastric ulcers, particularly when such are treated by the continuous alkalinization method first proposed by Leube, and frequently since then resurrected under a score of names. To combat the state of affairs subsequent to alkaline exhibition, the patient's stomach must of necessity be washed frequently or increasingly greater quantities of alkali must be given to overwhelm the stomach's defensive mechanism; then there follows physiological fatigue or exhaustion of the acid-secretion mechanism. It is a common observation that such patients as are treated for ulcer by the overalkalinization procedure always require frequent gastric lavage to insure their comfort. This frequent lavage is to be condemned not alone because it acts contrary to the fundamental principle requisite for healing, namely, rest of the affected part, but also because it creates distress in patients already undernourished, nervously and physically wearied, may be the cause of serious accidents and, moreover, is an unwarranted procedure scientifically. To those who, fluoroscopically, have watched the behavior of a stomach during lavage it is self-evident that the manœuvre defeats this primary principle of healing. Commonly, lavage is accompanied by vigorous gastric contractions; these persist not only during the procedure, but frequently persist for an appreciable time afterward. If dieting and general management are planned as above outlined lavage is not demanded for comfort. In the past eleven years I have not employed lavage therapeutically in ulcer cases more than a dozen times. Lavage is so rare a procedure in my clinic that my associates and patients consider it as almost contraindicated. It can be readily judged how a treatment, of which lavage does not form a prominent feature, contributes much to a patient's peace of mind and shortens the period of hospital incarceration.

Recent reports from the Mayo Clinic and from other institutions, where the treatment of true peptic ulcer by the continuous overalkalinization method has been tried, indicate that certain



patients to whom large quantities of alkali are given develop severe toxic symptoms. Even when large doses of alkali have been administered, gastric acidity is not noticeably or permanently reduced. Moreover, many of these patients develop toxic symptoms, as dizziness, headache, nausea and vomiting. That this is really a toxemia, the consequence of administering excess alkali, may be proved by study of the blood chemistry. Hardt reports that under alkaline ulcer regimen the blood urea may increase six times, blood carbonates practically doubled and creatinin increase more than 100 per cent. Of 30 patients thus treated in Hardt's department at the Mayo Clinic, fully one-third developed symptoms of toxicity as shown clinically and by study of the blood chemistry. Some of these toxic patients exhibited definite tetany. This phase has been commented upon recently by Tisdall, of the University of Toronto. He has shown that these toxic reactions result from increase of the bicarbonate ion of the blood, while there is no evidence of disturbance in calcium-phosphorus ratio of the blood. MacCallum and his co-workers have reported similar blood changes. Old, feeble patients, the subjects of arteriosclerosis, are especially likely to exhibit toxic evidences of overalkalinization; but these do not exclusively form the group so affected.

8. *Administration of Medicines.* It is doubtful if any kind of medicine has a direct healing effect upon peptic ulcer. In our service medicines are administered largely to counteract discomfort due to three main causes, namely: (1) Painful gastrospasms; (2) accumulations of overacid gastric contents associated with peristaltic unrest; (3) pain associated with perforation or ulcer progression.

(a) *Painful Gastrospasms.* These are usually controlled by carrying out the dietetic principles which I have above outlined. The chewing of paraffin wax relaxes the pyloric spasm largely through stimulating a proper swallowing reflex and by fatigue of hunger-like contractions. Certain types of case in which there is an individual vagus hypertonia, or where ulcers are located at or near the orifices, demand the exhibition of antispasmodic medicines, such as atropine, tincture of belladonna, or bromides. In the early stages of the treatment, when the stomach is being kept as free as possible of contents, atropine may be given hypodermically or tincture of belladonna or bromides may be dissolved in the nutrient enemata. Later, when food is being given by mouth, tincture of belladonna, in doses of from 5 to 15 drops, may be administered fifteen minutes before feeding and as frequently as three to six times daily. We have not found useful, as analgesics, large doses of such so-called "protective" medicines as bismuth and olive oil. These medicines doubtless act by affecting the rate and intensity of peristalsis, although they may have some effect in certain cases by direct action upon the ulcer. At times

orthoform, given in 10 grain doses, in warm water, is an efficient local anesthetic, when it is able to come in direct contact with an open ulcer.

(b) *Relief of Overacid Gastric Accumulations.* For this purpose sodium bicarbonate is contraindicated, since its administration results in the production of annoying accumulations of carbon dioxide with resultant gastric retention or painful belching, and because its neutralizing value is comparatively low. Large quantities of bicarbonate of sodium are necessary to give relief, and the administration of such, secondarily, produces excessive gastric secretion. Toxic signs most commonly follow the exhibition of huge doses of the carbonates of soda. If alkalies are indicated better results are obtained by the exhibition of frequent small doses of a fluid form, as milk of magnesia or solutions of calcined magnesia. When alkalies are used the ordinary patient is very comfortable when from 5 to 10 grains of calcined magnesia are given every two or three hours. Many cases require no exhibition of alkali if the physiological principles above outlined form the basis of the treatment. As I have mentioned, only on very rare occasions is it necessary to employ gastric lavage. When it is employed warm Carlsbad water (1 dram of artificial Carlsbad salts to 1 quart of water) may be satisfactorily used.

(c) *The Acute Prostrating Pains of Perforation of Ulcer Extension.* These are best controlled by the administration of morphine hypodermically, rest in bed and hot compresses to the abdomen. Prompt and skilled surgery offer the patient the greatest hope for relief in such crises.

9. *Hemorrhage.* Constant seepage, demonstrated either microscopically or clinically, is an indication for early abdominal section. Intermittent seepage may be controlled best by rest in bed, morphine hypodermically, intravenous injections of fresh horse serum or by copious transfusion of whole blood after the methods suggested by Kimpton and by Percy. In acute hemorrhage, accompanied by vomiting, prompt lavage of the stomach with water at 100° F. frequently stops both the vomiting and the hemorrhage. The exhibition of morphine, rest in bed and whole blood transfusions generally prevent recurrence of hemorrhage. In this class of case, however, surgical intervention should be resorted to early, and this especially if, in a given patient, frequent, copious, prostrating hemorrhages occur.

10. *Bowels.* During the early period of treatment simple soap-suds enemata may be administered every second day. After the second week, morning doses of phosphate of soda or of Carlsbad salts in hot water may be given. In chronic cases, liquid paraffin given in equal quantities of warm cream result in easy motions, and the paraffin appears to have certain protective value upon the ulcer-bearing area.

11. *Lues*. When it is suspected that lues is an important etiologic factor specific therapy should be vigorously pushed. Ulcer, clinically, of the infectious type may be helped toward healing by autogenous vaccines, the material for cultures being obtained from teeth roots, tonsils, sinuses accessory to the nose or from biliary tract drainage, *per duodenum*.

12. *Anemia*. Anemic patients usually require the exhibition of iron and arsenic in full doses if their tissues generally are to be expected to respond by maximum healing at the local gastric fault. Patients who come to our service greatly undernourished, with dry skin and mucosæ and exhibiting red counts as low as 3,500,000 have their bloods typed, and without loss of time consequent upon attempts to improve the blood by drugs, given spaced transfusions of 600 to 1000 cc of whole blood by means of Percy's modification of the Kimpton-Brown tube. It is remarkable how rapidly even desperate cases progress to healing after these initial constitutional boosts.

**Summary.** 1. Results of the non-surgical treatment of peptic ulcer have proved unsatisfactory because relief of symptoms and signs has been regarded as indicative of cure of the affection. Follow-up records of peptic ulcer patients demonstrate that symptom subsidence is not necessarily proof that the ailment has been healed permanently. Grave complications may occur when the subject is symptom-free and apparently physically vigorous.

2. The etiology of peptic ulcer is varied: subinfections, circulatory visceral disturbances, lues, neurological or endocrine imbalance, occupational hazard and trauma would appear to be types of anomaly leading to a systemic or constitutional fault, a local gastric manifestation of which takes the form of peptic ulcer. Considered from such viewpoint, gastric ulcer presents features suggestive of its being a self-limited local lesion.

3. There seems to be no evidence that ulcer is caused by alterations in gastric chemism or that its presence or course, fundamentally, are influenced by variations in the HCl-pepsin content of the gastric juice. The clinical symptoms coincident with uncomplicated ulcer are not explainable on the basis of abnormal secretory function; severity of symptoms bears little, if any, relationship to quantitative or qualitative variation in the acidity of gastric juice. "Hyperacidity" does not mean ulcer, nor does ulcer indicate "hyperacidity."

4. When ulcer is not complicated by such pathological phenomena as stenosis, perforation, gross hemorrhage or malignancy, the associated gastric digestive syndrome is most satisfactorily explained by regarding symptoms and signs as indicative of gastric, motor disturbances. The chief factors concerned with such abnormal gastric motor anomalies are: (1) Interference with the normal orderly peristaltic interrelationships between cardiac and pyloric sphincters,

and (2) between the activity of these sphincters and true gastric peristalsis. The effect of such failure of peristaltic coördination is increase in gastric tone and of intragastric tension.

5. It has been shown that gastric motor function is influenced by the kind of food intake. Carbohydrate demand the least motor or secretory work from the stomach. Such feeding lengthens the interdigestion phase of gastric diastole and secretory rest. The recognition of this physiological phenomenon establishes a fundamental starting place in the institution of a rational regimen for the non-surgical treatment of peptic ulcer.

6. Statistics of the results of gastric ulcer treatment are valueless unless definite proof is adduced that ulcer actually were present during the exhibition of any special regimen. Much of the literature which has been concerned with "ulcer cures" is worthless, because no proof is submitted which establishes that gastric ulcer existed in the patients under treatment. Any intra-abdominal pathological lesion or any systemic disturbances capable of initiating gastric motor incoördination, whether or no such be accompanied by secretory faults, or increased intragastric tension is capable of giving rise to "ulcer-like" symptoms; these require discriminating judgment to separate them from the digestive disturbance concomitant with true peptic ulcer. Ulcer diagnosis rests on a nice balancing of facts returned from clinical history, physical examination and roentgen observation.

7. When ulcer has been proved to exist, success of therapy is strictly dependent upon selection of instances for surgical or non-surgical treatment according to the pathology present. Unless luetic, little hope of non-surgical cure can be held out when ulcers are accompanied by obstruction, gross scar, and lesion of crater type, or have bled freely or exhibit malignancy.

8. A method of non-surgical, clinical management of selected cases is described. It aims, rationally, to take clinical advantage of established gastric physiological principles, especially, should peptic ulcer be accompanied by provable departure from the normal sequence of gastric motor function. It emphasizes, particularly, the necessity for attempting to bring about in the stomach physiological rest: motor and secretory. Thus it brings into the non-surgical clinical regimen of peptic ulcer, the primary principle of healing so thoroughly established surgically as essential for the repair of tissue damage in general. Further, the form of treatment advanced takes into consideration the systemic or constitutional inception of peptic ulcer and disregards the ancient theory of abnormal gastric chemistry being a factor against ulcer repair. Alkalies or other drugs and gastric lavage play a very minor part in the regimen described.

9. The treatment suggested has the advantages of being simple, inexpensive, easily borne and it shortens the period of hospital incarceration. In selected instances it permits unimpeded ulcer healing.

**THE REACTION OF THE PARATONSILLAR TISSUES TO  
TONSILLECTOMY: A STUDY IN THE ETIOLOGY OF  
POSTTONSILLECTOMY PULMONARY ABSCESS.\***

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**Introduction.** Since the appearance, eleven years ago, of Richardson's<sup>1</sup> paper there has developed, especially in the last few years, a deep interest in the incidence of lung abscess as a sequel to tonsillectomy. A recent comprehensive study of the situation, based on a widely circulated questionnaire, has been made by Moore,<sup>2</sup> who gathered reports of 202 cases. Among his conclusions are the following: "The vast majority of cases are of inspiratory origin because of (a) time of development and (b) involvement of the lower lobes of the lung in 60 per cent of the cases (right lower, 41 per cent; left lower, 19 per cent), being almost the same relative incidence as in cases of inspired foreign bodies.

"Blood-stream transmission of infected material, causing pulmonary abscess, occurs, but in a relatively small number of cases. Lymphatic extension is a rare mode of infection."

**Possible Pathways of Infection.** With this dire sequel occurring so frequently, and it cannot be questioned that it happens oftener than even Moore's paper would lead us to think, the thoughts of all interested must turn toward the reason or reasons for its occurrence and the adoption of methods of prevention.

The infection must reach the lung either (a) by way of the trachea and bronchi (bronchogenic), (b) by way of the venous system (hematogenic) or (c) by way of the lymph channel (lymphogenic). The writers of this paper instituted this study with no preconceived theory as to which pathway is the preponderating one, but they were of the opinion that the likelihood of the inhalation method of infection has been taken too much for granted. The fact that in Moore's series of 202 cases 39 (approximately 20 per cent) were secondary to operation under local anesthesia strengthened this view.

**Influence of Complete Tonsillectomy upon the Incidence of Lung Abscess.** It was in 1912 that attention first was drawn to lung abscess as a sequel to tonsillectomy. And it was about that

\* Read at the Forty-fifth Annual Meeting of The American Laryngological Association, held at Atlantic City, N. J., May 16, 17 and 18, 1923, and before the College of Physicians of Philadelphia, December 5, 1923.

time that the so-called "tonsillotomy" was being discarded in favor of complete removal, including the capsule. Possibly this is not a pure coincidence. Dean<sup>3</sup> says, "In my experience the infections have been much more frequent and severe since I have been performing tonsillectomy and not tonsillotomy." The infections he refers to are those in the immediate region of or adjacent to the tonsil. The incomplete tonsil operation, whether performed by guillotine, punch or what not, invariably left behind a mass of tonsil tissue walled off from the throat by a very firm and capable capsule. The raw surface left after operation was composed only of tonsil tissue with its associated vessels. No injury had been inflicted or infection implanted upon the muscle or other deeper structures of the pharynx, and no vessels of the tonsillar and pharyngeal region were traumatized or severed. In those days the use of a general anesthetic was universal and no suction appliance was in use, and yet posttonsillectomy lung complications were neither noted nor reported.

**Lung Infection of Bronchogenic Origin.** Let us consider for a moment the question of air-route infection. A fair fundamental question would be this: Is the lung very susceptible to infection through the air passages? The answer is, It is quite probable that the lung possesses inherently a highly protective margin of safety. This is evidenced by the fact that many injurious objects, notably bacteria, are daily being inspired under many and varying conditions with no deleterious result. General anesthesia offers a good opportunity for plugs of mucus and clumps of bacteria to enter the respiratory spaces, thousands of cases with dirty mouths are being etherized, but postoperative pneumonia is not as common as the possibilities thus afforded would lead us to anticipate. For example, in Cutler and Hunt's<sup>4</sup> 1920 series of 1604 operations there were but 7 cases of bronchopneumonia and 1 of lobar pneumonia occurring as complications. In these 8 cases local anesthesia was used once (in the lobar pneumonia case), gas-oxygen four times and ether three times.

Moreover, the production of experimental pneumonia by the atomizing of bacteria into the trachea has proved very difficult of attainment. It has succeeded regularly only when very large doses or highly virulent organisms have been used and when they have been introduced by puncturing the trachea through the skin of the neck.

The question might be put more broadly: Are unbroken or even broken mucous membranes reasonably subject to septic invasion? For example, is an abscess of the nasal septum not a very rare condition? How many rhinologists have seen an abscess of a turbinated body, and this even considering the abrasions and open pathways for infection caused by the common habit of finger removal of crusts from the nose? How many cases of foreign

body in the bronchial tree, the esophagus, the eye, the urethra or the intestines are followed by abscess? Very few! Of course, the bronchial and pulmonary mucosa may be less tough than that in the other locations mentioned; but even granting this, when a lung inhales some septic material in which are microorganisms to which the individual is probably partly immune, why should we necessarily assume that this inspired material is the cause of an abscess to the exclusion of other possible sources of infection?

**Lung Infection of Hematogenic Origin.** On the other hand, postoperative pulmonary embolism, following surgical procedures in the abdomen and elsewhere, is a common condition. Many of these cases are badly shocked and die promptly, because the embolus comes from a large vessel and blocks off a large branch of the pulmonary artery and a large area of lung. Even if the embolus is a septic one, death in such cases usually occurs before an abscess has time to form.

In the field of general surgery the thoughts of investigators are turning decidedly toward the embolic nature of postoperative lung complications. A careful and exhaustive study recently has been made by Cutler and Hunt<sup>5</sup> of a year's cases in the surgical wards of the Peter Bent Brigham Hospital, where a specially careful watch has been kept for the appearance of postoperative lung lesions. As the result of improved methods of case-watching and study, the percentages of such complications found has more than doubled in five years. Along with this naturally has come a drop in mortality percentage, because many small lesions have been discovered, lesions which appeared and disappeared with but few symptoms.

During 1920, 1604 cases were operated upon, and "63 of these patients developed a pulmonary complication that might be attributable to the operative intervention or to the anesthetic. There were 5 deaths among these 63 cases. Thus in 3.93 per cent of the cases (1 in 26) a complication developed and 0.3 per cent (1 in 321) patients died from one of the complications."

In this group of 63 there occurred 1 case of lobar pneumonia, 7 of bronchopneumonia, 16 of bronchitis, 2 of exacerbation of tuberculosis, 2 of pleurisy, 1 of empyema, 32 of *pulmonary infarction* (italics ours) and 2 of pulmonary embolism. Thus, even in a general surgical clinic approximately 1 case in 50 was complicated by an infarction of the lung, which shows that this form of pathological lesion occurs more frequently than is generally thought.

Among their conclusions are the following:

"Irritation and aspiration due to inhalation anesthesia may be the cause of a small percentage of postoperative pulmonary complications.

"The fact that these complications occur with local anesthesia, with inhalation anesthesia in the most expert hands and in a

definite relation to the mobility of the operative field, is taken as evidence against the importance of the irritation of inhalation anesthesia in the production of these lesions."

W. J. Mayo<sup>6</sup> states that septic emboli from the operative field are a common cause of secondary pulmonary complications. He laments that these complications are too frequently attributed to the anesthetic, and says that they are quite as frequently found in cases in which local anesthesia is employed. Many other surgeons could be quoted to the same effect.

Among otolaryngologists the possibility that these lung lesions are of embolic origin is not entirely a new one. Of those who might be quoted in this respect are Richardson, Porter, and Simpson and Noah.

Richardson<sup>7</sup> in his 1912 report describes 2 cases under the title of "Septic Infarct of the Lung."

Porter<sup>8</sup> says: "There exists a complicated network of veins, the plexus tonsillar and the plexus pharyngeus, which cover the outer walls of the pharynx and the tonsillar cavities, receiving blood from the tonsils, tonsillar pillars and pharyngeal walls. These vessels are exposed and always injured even in the gentlest operative work. This too is a field impossible to protect from germ-laden saliva and pus. It is therefore not difficult to believe that infected emboli could be dislodged from veins thrombotic from trauma and infection, located in an area active in every attempt at speech and swallowing. I feel that there can be no doubt that infected emboli travel direct to the lungs and cause certain cases of pulmonary abscess."

Simpson and Noah<sup>9</sup> state, "The writers believe that aspiration does not account for the production of lung abscess in the 2 cases reported." They conclude: "1. During or following operation septic material enters the veins, passes through the right heart to the lungs and there finds, in the presence of a tuberculous lesion, suitable soil for the production of an abscess.

"2. The possibility of aspiration of infected material as a cause of pulmonary abscess is not to be denied, yet we believe that more cases occur as a result of hematogenous infection than is generally supposed."

**Answers to Arguments Favoring Bronchogenic Origin.** A common argument in favor of the aspiration of infected matter as a cause of lung abscesses is that in location (preponderatingly on the right side and in the lower lobes) they correspond quite closely to that of foreign bodies. We believe this argument is not as definitive as appears on the surface, for the following reasons:

1. Foreign bodies have no monopoly of localization in the right lung and its lower lobe. Pulmonary emboli, especially massive ones, seek the right side to even a greater degree than do foreign bodies. An abstract<sup>10</sup> of an article by Capelle<sup>11</sup> states that:



"Pulmonary infarction and embolism (*massive*—authors) was stated to have occurred in 15 among 10,000 operations, but many cases called postoperative pneumonia are really instances of small pulmonary infarctions. A distinguishing sign is the bright-colored blood expectorated as compared with the rusty sputa of pneumonia."

Then follows a sentence having marked bearing on the question we are discussing: "Thirteen presented changes in the back and front of the lower pulmonary lobes, and in only 2 were the signs restricted to the left lung." Thirteen out of 15 were in the right lung and all of them in the lower lobe! Does this not cast doubt upon the location of lung abscesses proving their inhalation etiology? So much for *large* emboli.

In searching the literature for data as to the localization of *small* infarcts we were unable to find definite figures. A letter of inquiry to Dr. Elliott C. Cutler<sup>12</sup> brought a generous and prompt response, and we are able to give his unpublished figures on this point. We herewith desire to express our deep appreciation of his kindness. His table is as follows:

#### DISTRIBUTION OF POSTOPERATIVE PULMONARY INFARCTION.

	1920 cases.	1921 cases.
Right upper lobe . . . . .	0	2
Right middle lobe . . . . .	2	1
Right lower lobe . . . . .	14	7
Left upper lobe . . . . .	0	0
Left lower lobe . . . . .	5	4
Both lower lobes . . . . .	2	1
Right upper and middle lobes . . . . .	1	0
Left upper and lower lobes . . . . .	1	0
Totals . . . . .	25	15

Cutler had accurate data on 40 of his cases. Of these 21 were in the right lower lobe only and 9 were in the left lower lobe only (21 to 9); 30 of the cases involving more than one lobe were located in the right lung and 13 in the left lung (30 to 13).

Welch<sup>13</sup> states that: "The course followed by an embolus in its travels is determined by purely mechanical factors, of which the most important are the size, form and weight of the plug; the direction, volume and energy of the carrying blood stream; the size of branches and the angles at which they are given off, and the position of the body and its members. In accord with these principles we find emboli in the lower lobes of the left lungs oftener than in the upper, and in the right lung oftener than in the left, the right pulmonary artery being larger than the left."

The size of the right pulmonary artery and right lung is to that of the left pulmonary artery and left lung as 4 is to 3. Therefore, an embolus leaving the right heart, other things being equal,

would have 4 chances of going to the right lung to 3 of going to the left, or in 100 cases 57 would go to the right and 43 to the left.

2. Another factor could be the course of the two pulmonary arteries as and after they leave the pulmonary aorta. Possibly the right pulmonary artery is in more direct line with the pulmonary aorta than is the left. We are at present studying this piece of anatomy, but are not yet ready to report.

3. The inhalation of bloody throat secretions during tonsillectomy is, in our belief, not precisely comparable to the dropping or inhaling of a foreign body into a bronchus. In the great majority of cases foreign bodies enter while their host is in an erect posture, and in dropping down the trachea they naturally would tend to enter the wider and more vertical right bronchus. On the other hand, during tonsillectomy, under ether, with the exception of certain parts of New England, the patient usually is in a recumbent position and gravity could have little or no bearing on the problem. Whatever enters the trachea is drawn in during inspiration and consists of frothy, bloody mucus and tonsil crypt contents. It moves up and down the larynx and trachea during respiration, and when a collection of this material reaches the tracheal bifurcation it is almost as likely to be inspired into the left lung as into the right.

4. A final argument against the general acceptance of the respiratory theory of these lesions is the fact that so many are reported as being sequential to operation under local anesthesia.

With these facts in mind it is at least conceivable that the inhalation theory, based upon a wider right bronchus with a more direct course in relation to the trachea, should be relegated to a less important place than it hitherto has occupied in the minds of otolaryngologists.

**Reason for and Plan of Present Communication.** With these thoughts as a working basis, it occurred to us that a minute study of the pharyngeal and cervical region following tonsillectomy would tell us exactly what happens there as a result of the operation. We hoped that examination of the peritonsillar tissues, and especially of those venous and lymphatic tissues which drain the tonsil area, might afford information as to the probable location of the *fons et origo* of lung abscess. We felt that we would be studying a region into which septic tonsil contents are squeezed during operation, which would be traumatized during operation, into which needle-borne septic sutures frequently are carried during operation and which is wide open to constant microörganismal infection after operation. Such conditions are ideal for the formation of septic thrombi which later could become detached and pass down the internal jugular vein into the right heart and thence into the lung. We felt also that there is hardly any place in the body where thrombi would be more likely to become detached,

because the contraction of the tongue and throat muscles during swallowing certainly would promote the loosening of vein clots and the starting of them on their way down the jugular, through the heart and into the lung.

The present communication is based upon the results obtained from operations upon animals. Our experiments were as follows: One animal we devoted solely to the identification of the tonsil lymph node, using Gerota's technic, as employed by Wood<sup>14</sup> in

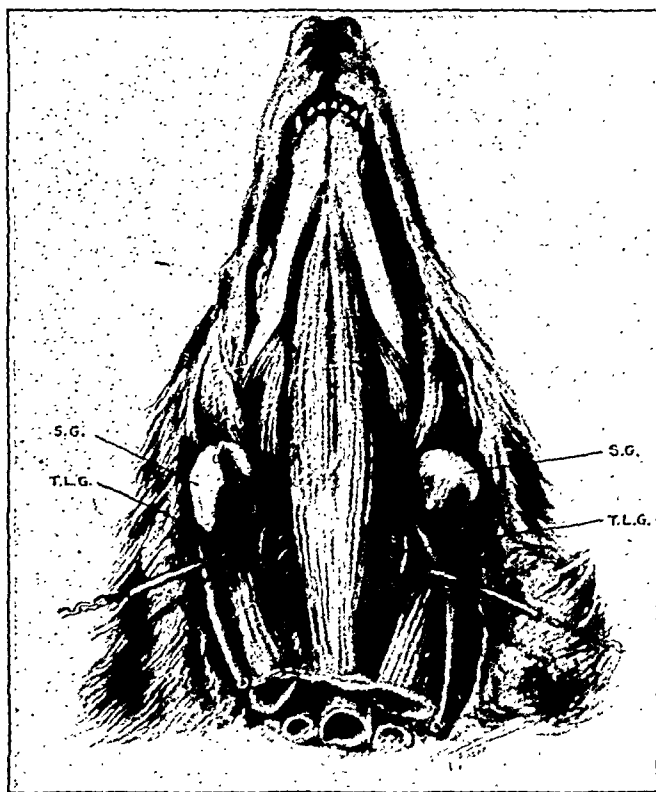


FIG. 1.—Author's drawing of a dissection of the neck, made after the tonsil region had been injected with a turpentine-ether solution of Berlin blue. The tonsil lymph node is shown, with its afferent lymph vessels. These vessels were traced back to the peritonsillar connective tissue. *TLG*, tonsil lymph node; *SG*, salivary gland.

his study of the same structure in man. The others were tonsillectomized. In one of them we removed one tonsil and left the other undisturbed, so that the tissues of the two sides subsequently could be compared. In the remainder both tonsils were removed: On one side two sutures were introduced and tied, while on the other an attempt was made to infect the raw surface by swabbing with bacteria. Before the sutures were passed they were soaked in a suspension of bacteria, these being actively hemolytic staphylococci and streptococci, the former having been isolated from the

blood of a case of staphylococcus septicemia and the latter from a case of acute pharyngitis.

Intratracheal ether anesthesia was used in each operation, and, in order to secure conditions well removed from the ideal, no antiseptic cleansing of the throat was done before operation and no sterilizing of hands, instruments or gauze was attempted. Two

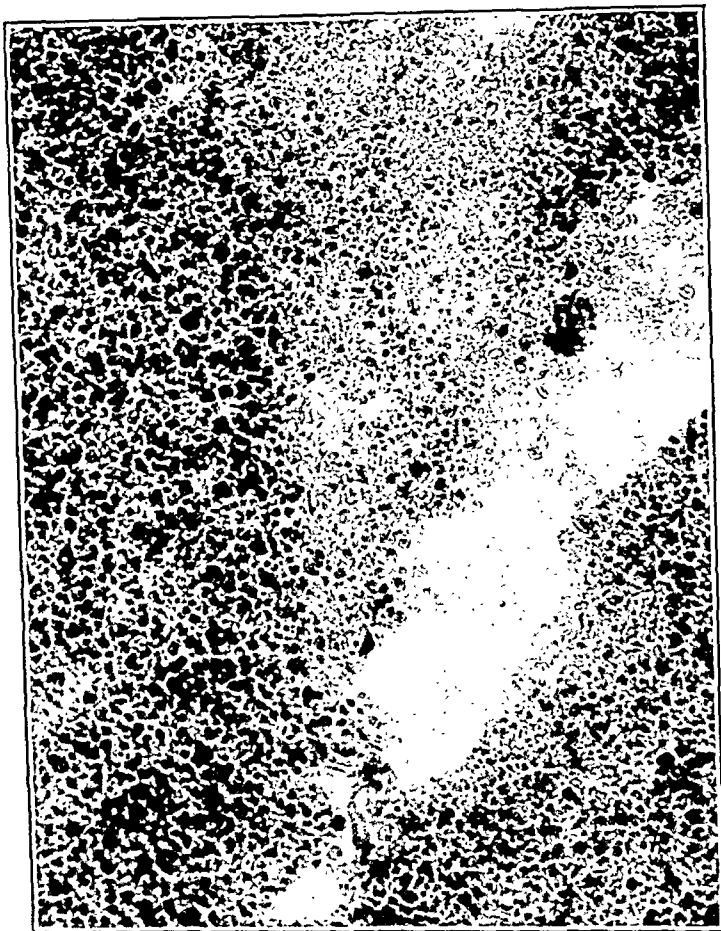


FIG. 2.—Tonsil lymph node, showing globules of pigment along cords. This specimen was taken from an animal which was killed one-half hour after the tonsil region had been injected with a turpentine-ether solution of Berlin blue. This was done to determine and identify the lymph node, which is next in series with the tonsil. It demonstrates how rapidly absorption from the tonsil into the lymph node takes place. The small globules of dye can be seen as innumerable black spots following the distribution of the lymphatic cords. No tissue stain has been used in this section.

of the animals were killed at the end of two days and the third after a lapse of four days. Various blocks of tissue were removed and studied histologically as well as for bacteria.

This part of the work was done in the Laboratory of Surgical Research of the University of Pennsylvania, and we are greatly indebted to Dr. J. Edwin Sweet for his helpful coöperation.

**Results of Present Investigations.** Study of our material, both gross and microscopical, has elicited the following facts:

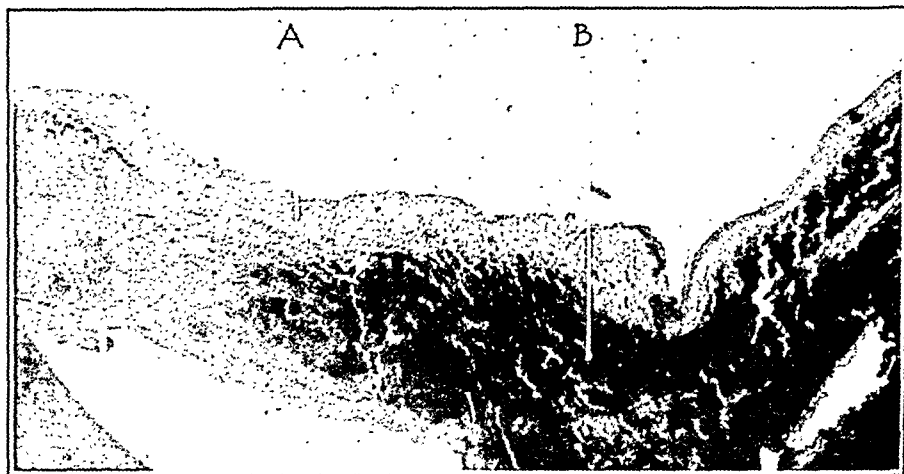


FIG. 3.—Tonsil pillar, showing submucous tissue distended with recent blood clot, two days after operation. This photograph illustrates one of the results of operative trauma on the tissue immediately adjacent to the tonsil. A, faucial mucosa and submucosa; B, muscular and fibrous tissue infiltrated with blood.

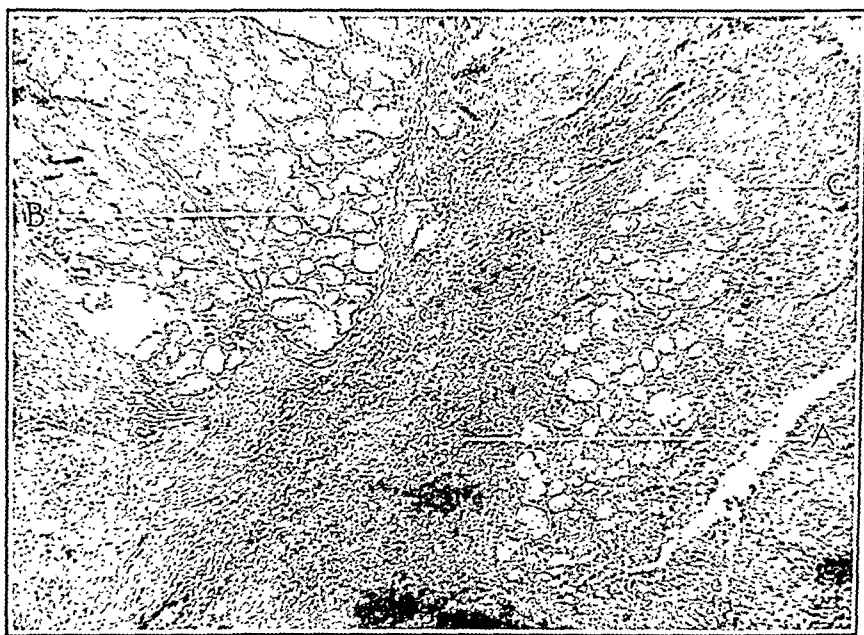


FIG. 4.—Salivary gland adjoining operation area. This specimen demonstrates hemorrhage into the gland as seen two days after operation. The hemorrhage shows as the dark structureless areas in the center and spreading out between the tubules. The pressure of the hemorrhage and the deprivation of blood supply have caused the gland cells to degenerate and the acini to lose identity; incidentally all parts lose contrast. A, hemorrhage; B, degenerating salivary gland, but some identity retained; C, more seriously destroyed salivary gland.

*The Tonsil.* The position of the tonsil in a narrow recess between and almost covered by the pillars, as depicted by Sisson,<sup>15</sup> was confirmed.

*The Tonsil Lymph Node.* The large lymph node lying under the occipitomandibularis muscle lateral to the pharyngeal wall and anterior to the sternomastoid was (Fig. 1) identified as the

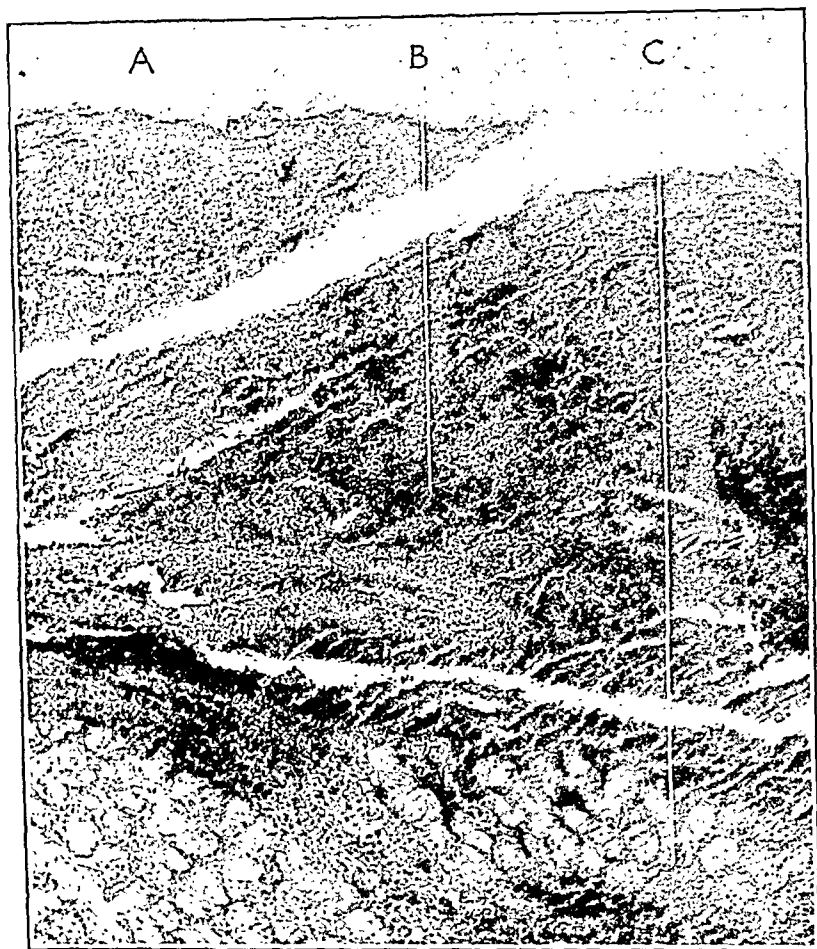


FIG. 5.—Operation field near salivary gland two days after operation. This picture shows hemorrhage and dense polynuclear and round-cell infiltration into the muscle tissue under the operation site and into the near-by salivary gland. A, raw operation field; B, muscle tissue with marked inflammatory cellular invasion; C, salivary gland with similar cellular invasion.

drainage node next in series to the tonsil. Turpentine-ether solution of Berlin blue injected into the tonsil was found to have drained rapidly (well under one-half hour) into this node. Lymph vessels were found, visible to the naked eye, connecting the lateral pharyngeal wall with this node. Dissection (Fig. 2) and microscopy of the tonsil revealed globules of the stain in the sinuses and along the cords of the tonsil, and also in the loose peritonsillar

connective tissue. In the lymph node (to be called hereinafter the "tonsil lymph node") it was found to some extent under the capsule, but mainly along the cords within the node.

*Local Postoperative Effects of a Purely Traumatic Nature.* The first effect of tonsillectomy, that of trauma, was found in our material principally as hemorrhage. There was a pouring out of blood (Fig. 3) not only into the tissues immediately subjacent to the operative field, but also in those lateral to it, under the intact epithelium, and extending well beyond the pillars of the

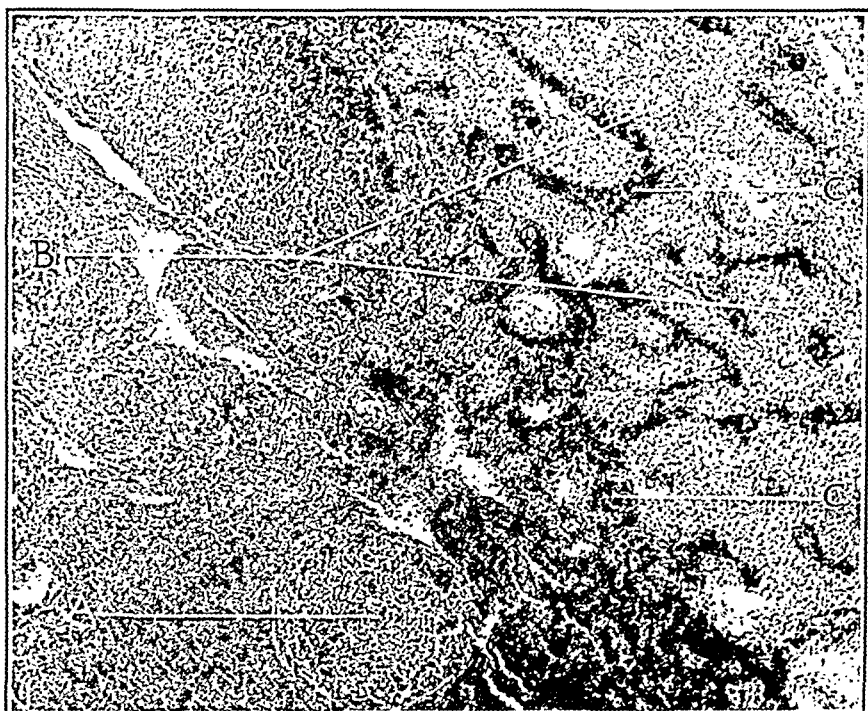


FIG. 7.—Section of the tonsil lymph node depicted in Fig. 6, *a*. The tonsil on this side of the body had not been removed. Specimen was removed two days after operation. While this node shows moderate activity in the follicles, all proportions are correct and the sinuses and cords are practically normal. A, follicle; B, sinuses; C, small normal cords.

tonsil (Fig. 4). In addition, hemorrhage was found in the adjacent salivary gland with resultant degeneration from pressure and impaired nutrition. Further reaction to the operative procedure was found in the form of round-cell and polynuclear infiltration, followed later by fibrino-cellular exudation, the latter varying with the infection (Fig. 5). This cellular infiltration reached the lateral and deep tissues, and among its sinister possibilities is destruction of these tissues, as happened to the salivary gland in these experiments.

Over the operation field a fibrino-cellular sheet was found, the



(a)



(b)

FIG. 6





superficial layers of which are progressively cast off, just as false (Fig. 10) membrane loosens, until the healing area beneath it is completely exposed.

*The Effect of Tonsillectomy upon the Tonsil Lymph Node without any Attempt Having been Made to Infect the Operation Wound.* Two days after operation blood was present in the tonsil lymph node. The node was swollen and, when sectioned, was found to be so full of fluid (Fig. 6) that the cut surface was wet and greatly

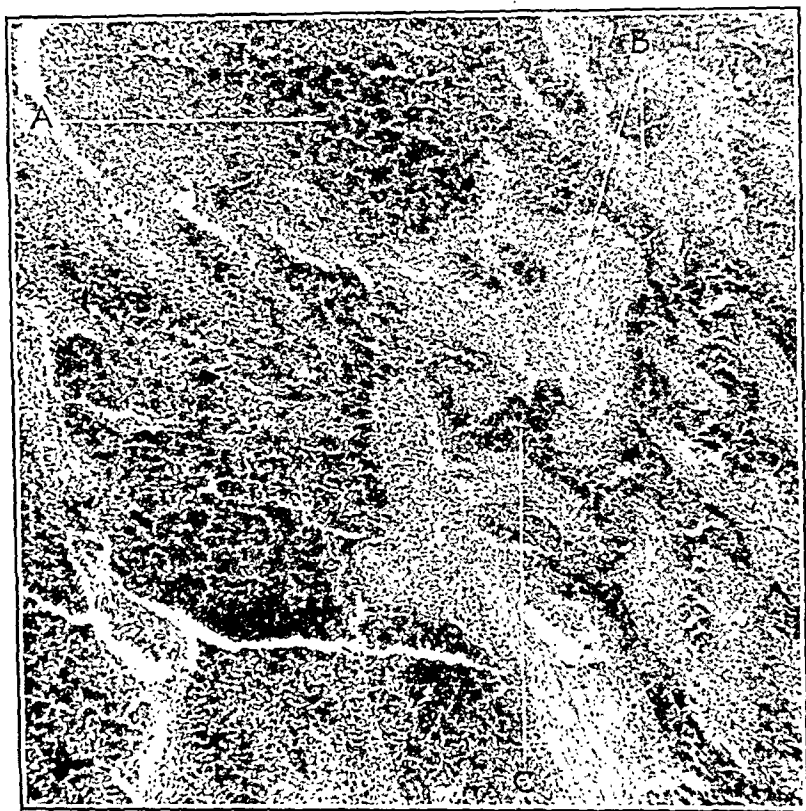


FIG. 8.—Section of the tonsil lymph node depicted in Fig. 6, *b*. The tonsil on this side of the body had been removed. Specimen removed two days after operation. The lymphoid tissue is very active and the markings are obscure, there being for instance no germ center in the two follicles in the picture. The sinuses are distended with blood, and the cords are wider than in Fig. 9. A, follicle showing activity; B, blood-filled lymph sinuses; C, cords.

congested. The node on the unoperated side was pale pink or yellowish and less wet.

Under microscopical study the node on the operated side was seen (Fig. 8) to be full of blood cells and their fragments, the sinuses especially being widely dilated. The lymphoid tissue itself was active in proliferation, but the follicular areas were not emphasized, there being instead a diffuse lymphocyte increase of all parts.

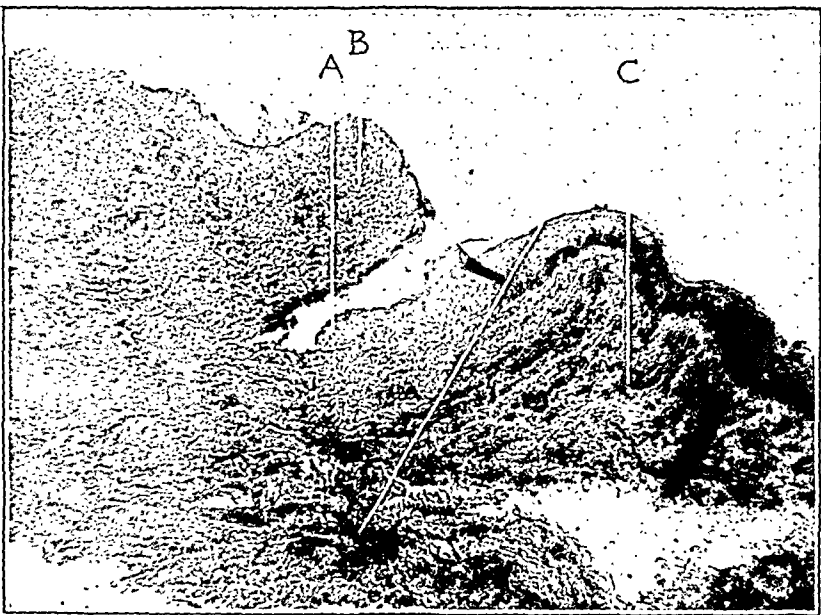


FIG. 9.—Edge of the operation site, showing postoperative exudate overlying the edge of the epithelium two days after operation. *A*, end of the epithelium at the edge of the operative field; *B*, edge of the postoperative exudate overlying, but here artificially separated from, the epithelium; *C*, blood under the epithelium at the site of the operated area.

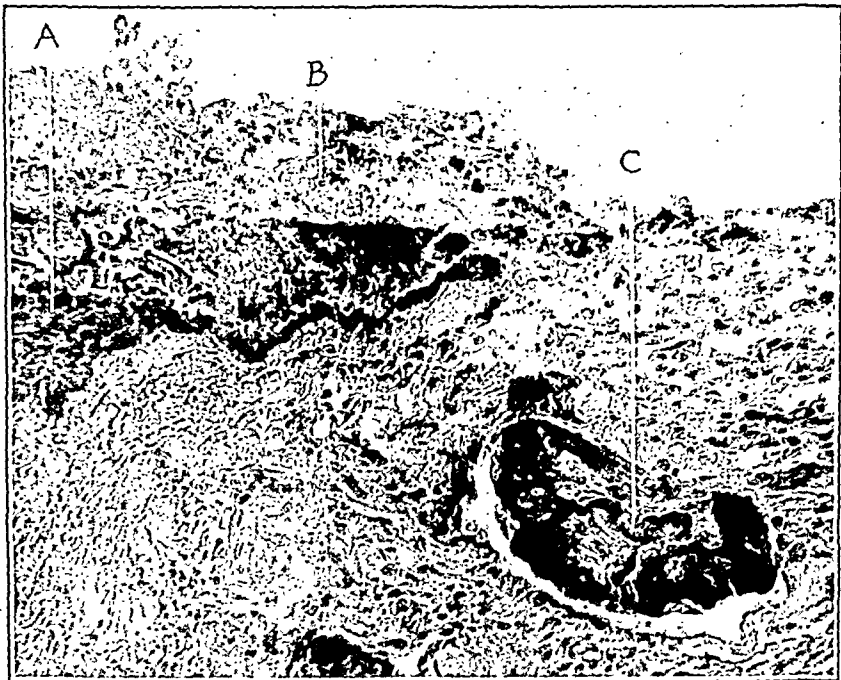


FIG. 10.—A portion of the operation field four days after operation, with the tissues stained for fibrin. The dark parts are fibrin. On the surface is an exudate consisting of two layers, a superficial light and a deep dark one. The former represents the actively degenerating part of the exudate, while the latter is the firm fibrinous exudate itself. The latter lies upon the healing operation base, and will itself later degenerate and be cast off. A well-formed thrombus lies in a vein just below operation area. *A*, fibrinous exudate; *B*, degenerated part of the exudate; *C*, thrombus.

On the unoperated side the node was found to be active in its (Fig. 7) follicular areas, but otherwise normal.

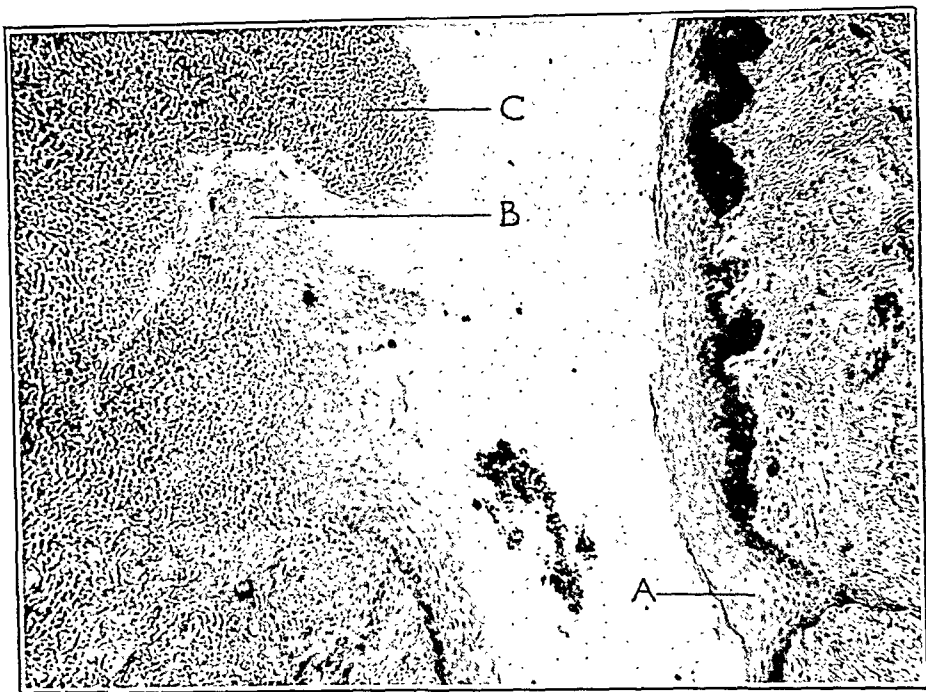


FIG. 11.—Tissue at the edge of the operation area, two days after operation. This figure shows the two lips of the wound, the one with undisturbed epithelium, the other at the cut edge where the epithelium is trying to spread but meets the exudate at the operation site. The epithelium is attempting to cover the raw surface but the exudate overlaps the proliferating surface cells. A, normal epithelium; B, inflamed epithelium at the edge of the wound; C, edge of the exudate overlying B.

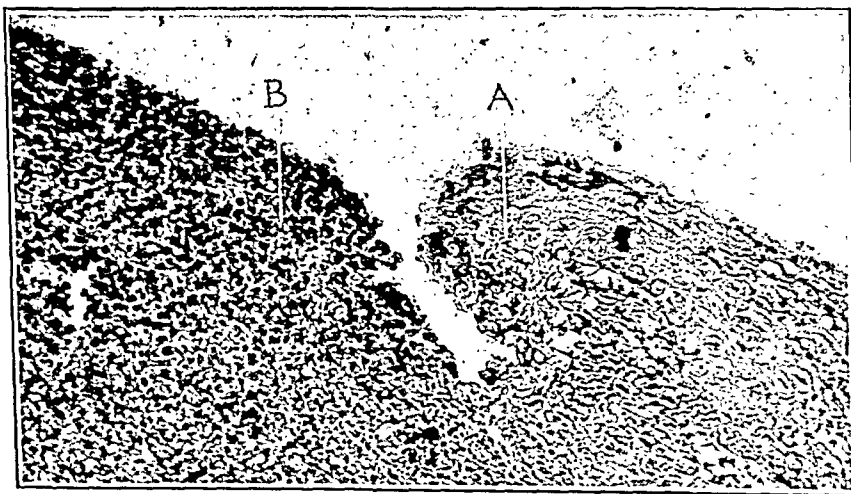


FIG. 12.—Edge of the tonsillectomy area, two days after operation. This figure shows the edge of the epithelium unable to make headway against the infected actively inflamed base of the operation site. A, edge of the epithelium; B, inflamed tissue showing the fibrino-cellular exudate developed at the operation site.

*The Peritonsillar Results of Tonsillectomy which are not Purely Traumatic and which were Found when the Wound had been Artificially Infected. At the area of operation there was found,*

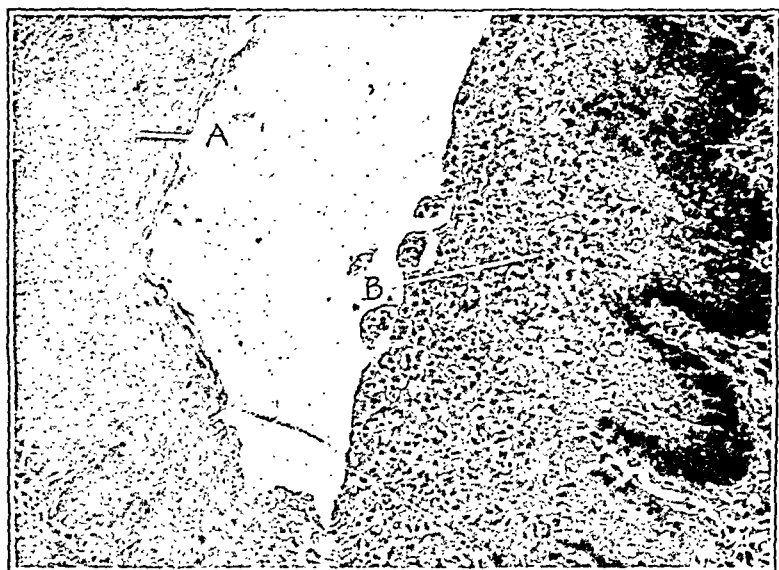


FIG. 13.—Fold in the mucous membrane adjoining the edge of the operation area, two days after operation. Normal epithelium at a distance from the wound. Actively inflamed epithelium adjoining the edge of the wound. A, normal epithelium distant from the wound; B, epithelium near the wound, showing active inflammation with many polymorphonuclears.



FIG. 14.—Base of operation site, two days after operation. This specimen shows dense infiltration, edema and a thrombosed vein. A, dense infiltration of round and polynuclear cells and much edema; B, thrombosed vein; C, thrombus artificially detached.

two days after operation, a well-developed fibrino-cellular exudate (Fig. 9). This not only covered the raw surface, but also extended laterally to overlie the edge of the adjacent epithelium. This exu-



FIG. 15.—Thrombus in a vein just under the operation site, two days after operation. At several points the thrombus will be seen to be quite free from the lining of the vein, but at most of its periphery it will be seen to be closely attached. *A,A,A*, wall of vein; *B,B,B*, thrombus; *C,C*, raw operation field.



FIG. 16.—Deep tissue beneath the operation site, two days after operation. This specimen shows vacuolated salivary gland cells, and separation with destruction of a small piece of salivary gland by cellular infiltration. It also shows edema and degeneration of a large area of muscle, small strands of which are recognizable. *A*, salivary gland with vacuolated cells; *B*, isolated island of salivary gland surrounded by cells and edema; *C*, degenerated muscle, strand remnants of which are seen at *D*.

date formed a barrier (Fig. 12) to the extending of the epithelium over the raw surface. In addition, when infection was present the stratified layers of epithelium were seen to be thickly beset with polynuclears (Fig. 13) and in a state of active inflammation, this decreasing as the distance from the operation site increased (Fig. 10). The exudate lay upon a tissue base characterized by a reactive cellular inflammation.

A noteworthy finding in this inflamed part was the congestion of all varieties of vessels and the frequency of thrombi, both near the surface and deep in the tissues (Figs. 14 and 15). These thrombi were attached to the vessel wall and were well developed by the end of the second day. No signs of softening were observed in any of them.

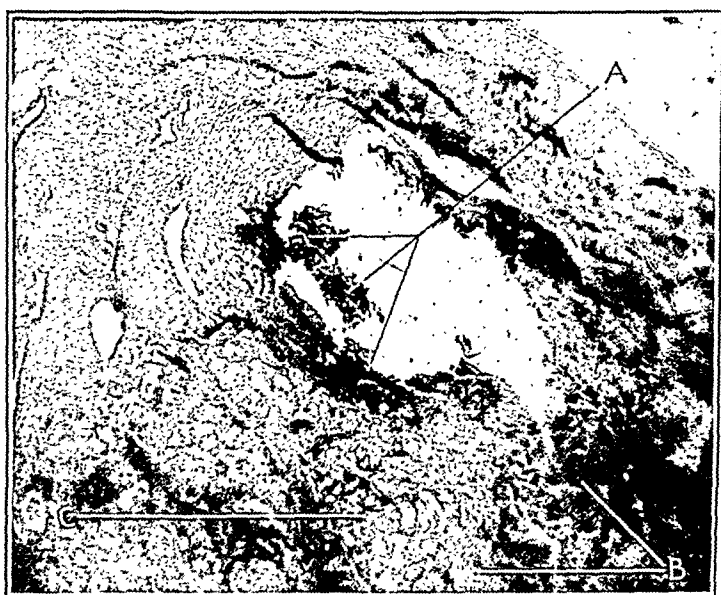


FIG. 17.—Silk stitch and adjacent area, under low magnification, four days after operation. Most of the stitch fibers have fallen out of the section. This picture shows a healthy reactive area around the stitch, with some degeneration of muscle and salivary gland tissue. *A*, fibers of the suture; *B*, degenerated muscle; *C*, degenerated salivary gland.

Study of the deeper tissues of the tonsillectomy area showed the inflammation to be similar to that near the surface, including a feature already noted, viz., the involvement of the salivary gland (Fig. 16). In addition the fibrino-cellular exudate was seen to extend well into the muscle tissue (Fig. 15), and many small thrombotic veins were here encountered.

*The Local Effect of Sutures.* The suture tracks were found to be surrounded by a mild fibrino-cellular reaction, highly cellular at the end of two days (Fig. 17), and showed signs of healing at the end of four days. The tissue caught by the stitch was com-

pressed and degenerated, particularly the muscle and salivary gland tissue (Fig. 18). Small patulous capillaries were found in the healing area, but the large veins usually were thrombotic.



FIG. 18.—This picture shows the stitch and its adjacent tissue, under high magnification, four days after operation. A, strands of the stitch; B, healthy reaction to the stitch, some round-cell infiltration in small groups, but no abscesses.

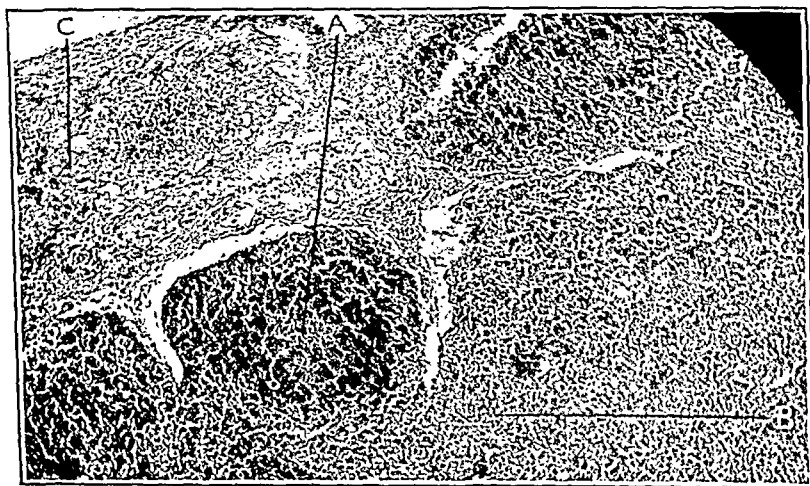


FIG. 19.—Tonsil lymph node, two days after operation, on the side of which infected stitches were used to close the wound of tonsillectomy. This node shows a very active hyperplasia, as indicated by the size and solidity of the follicles, a degree of compactness of the intervening lymphoid tissue great enough to obliterate the sinuses. In addition, there are congestion of the capsular vessels and distention of the lymph ducts. In certain of the capsular lymph channels some swelling and degeneration of the lining were found. Bacteria were found in these lymph ducts. A, hyperplastic follicle; B, solid cordal area without visible sinuses; C, swollen, congested and edematous capsule.



*The Tonsil Lymph Node after Operation Plus Artificial Infection of the Operation Wound.* The tonsil nodes after an infected operation were very large, soft, wet and irregularly congested, especially at the capsule (Fig. 19). Under magnification a very marked hyperplasia was found, differing greatly from conditions depicted in Figs. 9 and 10. The follicles showed large germ centers and the cords were crowded with mononuclears. The sinuses were compressed almost to extinction by the lymphoid increase or were filled with large and small mononuclears (Fig. 21), as well

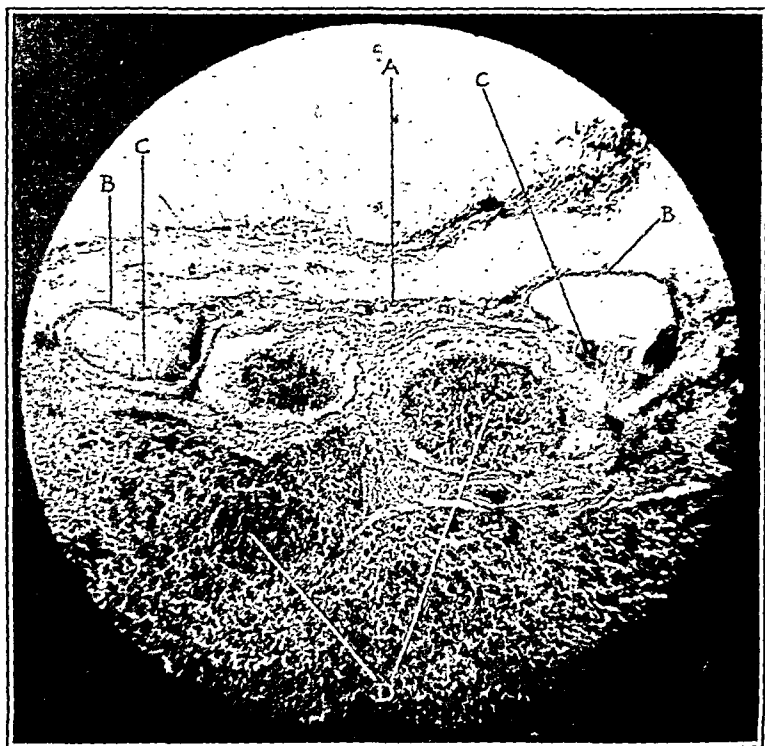


FIG. 20.—The same lymph node as that from which section shown in Figs. 19 and 21 were taken. It shows dilated lymph vessels with postmortem clots. A small group of bacteria was found in one of these clots near the lining of the vessel. Solid hyperplastic follicles of the node lie under the capsule. A, capsule of the lymph node; B, B, lymph vessels; C, C, coagula; D, follicle.

as with endothelioid and polynuclear cells. This last change was best seen near the hylum of the node. In addition, the increased size of the lymph vessels was quite notable. They were greatly dilated and were almost completely filled with a hyaline post-mortem lymph clot (Fig. 20), this being especially notable in the capsule. Bacteria were found in or near the lining of these vessels.

It should be stated in this connection that a superior mediastinal lymph node of one animal showed a similar hyperplasia. There were present also dilated lymph vessels, small hemorrhages

and very marked degeneration of the follicular centers. Bacteria were not surely found.



FIG. 21.—The same lymph node as that from which sections shown in Figs. 19 and 21 were taken. Central area of the node under high magnification. This specimen shows the cellular richness of the central sinuses. Numerous lymphoid cells of all varieties, polymorphonuclears and large mononuclears of endothelioid proportions were found in the well-crowded spaces. The cords are very thin at this point. A, a crowded sinus; B, the end of a small cord.

*Bacterial Distribution.* Bacteria in those cases which were artificially infected were found with ease in the stitches and in the

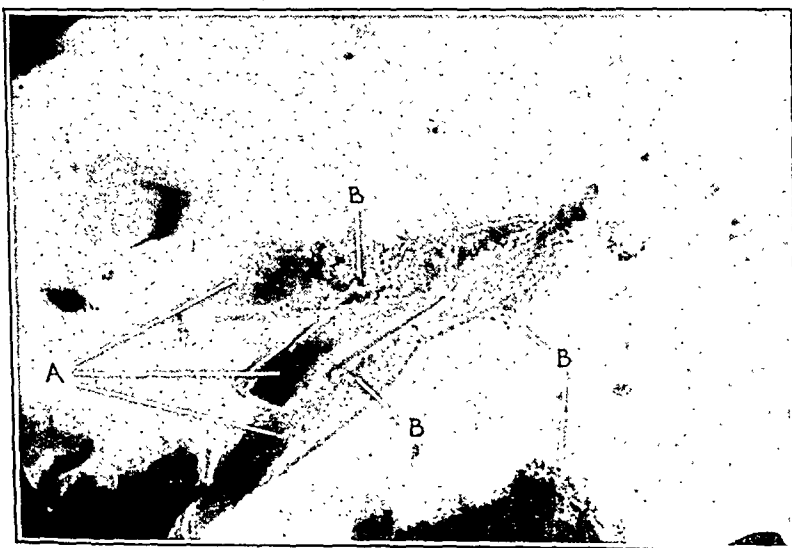


FIG. 22.—A strand of stitch with bacteria in it, four days after operation. (Oil immersion exposure.) A, fibers of silk; B,B,B, bacteria.

area immediately surrounding them (Fig. 22). As distance from the stitch region increased the microorganisms became fewer and

fewer. They were traced along one tissue split into a muscle area (Fig. 23), and also were found in a salivary gland.

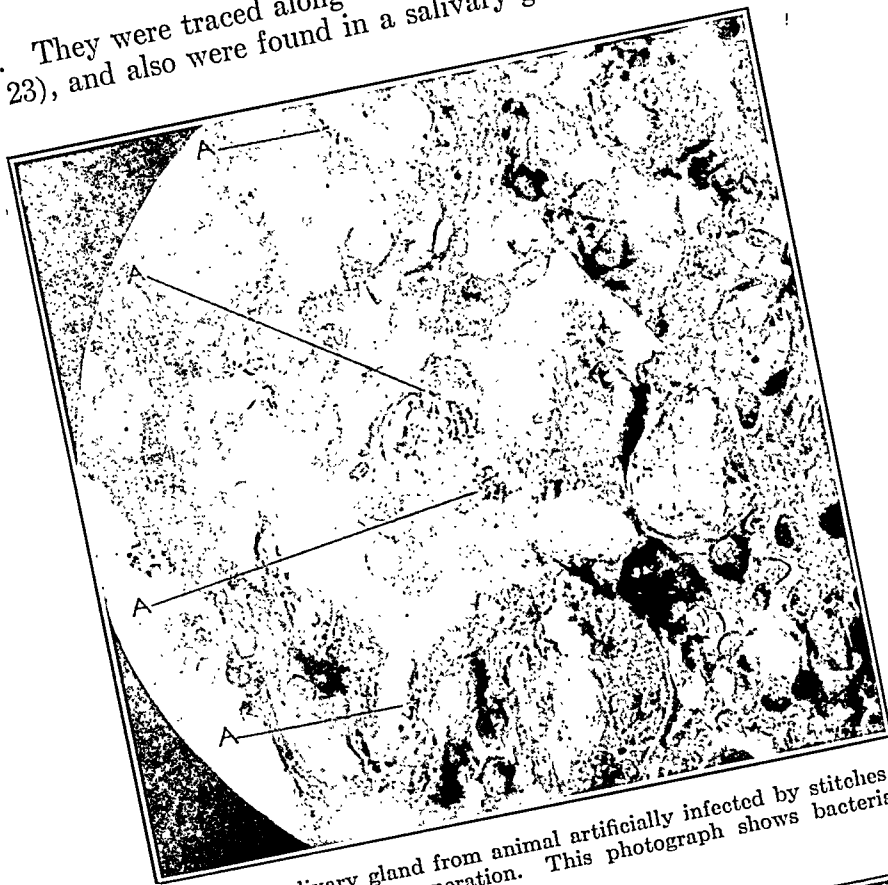


FIG. 23.—The salivary gland from animal artificially infected by stitches soaked in cultures, four days after operation. This photograph shows bacteria singly and in groups. A,A,A,A, bacteria.

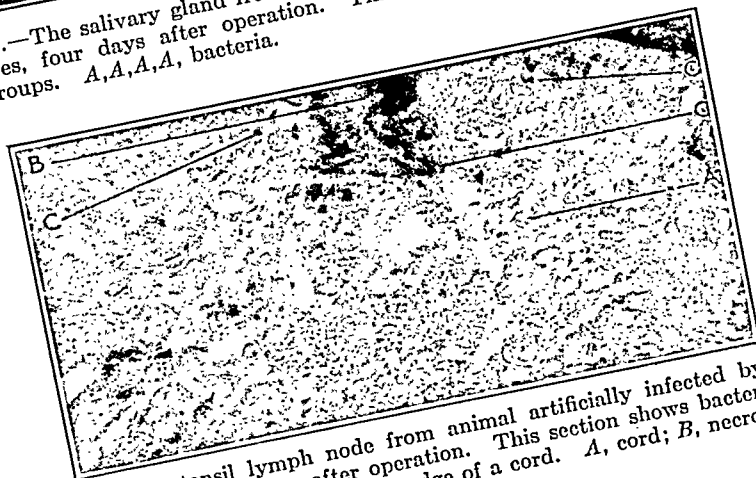


FIG. 24.—The tonsil lymph node from animal artificially infected by stitches soaked in cultures, four days after operation. This section shows bacteria on the edge of a cord and in a necrosis at the edge of a cord. A, cord; B, necrosing area; C,C,C, bacteria.

In the tonsil lymph node bacteria were present in pairs and in small clumps. They were found in the dilated capsular lymph

vessels (Fig. 24), in the subcapsular (the so-called "marginal") sinus and in the interior sinuses near the edges of the cords.

They were not found with unequivocal certainty in the thrombosed vessels.

**Summary of Results.** Injected material found its way from the tonsil to the first drainage lymph node in half an hour or less.

Tonsillectomy traumatism was manifested not only at the immediate operation site, but also in the collateral tissue in the form of hemorrhage and cellular infiltration.

The surface of the wound was covered with a fibrinous exudate, the outer layers of which were progressively cast off.

The tissue reaction at the site of operation was degenerative and fibrino-cellular, the former appearing at once, the latter being in part the result of traumatism and in part the natural successor to degeneration, and therefore the early stage of repair.

Exudate of a fibrino-cellular character was found deep in the tissues, with resultant degeneration of muscle and salivary gland tissue.

Many venous thromboses were found both near the surface and deeper.

The tonsil lymph node reacted to moderately clean operative procedures by caring for the extravasated blood and by mild hyperplasia.

To a purposely infected operation the reaction of the lymphatic tissue was very marked, so much so that the lymph current probably was obstructed.

Each attempt at artificial infection succeeded and important structures, such as muscles and glands, were found to have been invaded by the microorganisms.

Bacteria were found easily in the surface exudate and in the vicinity of infected stitches. They also were found in the salivary glands and in the tonsil lymph nodes.

When bacteria-soaked stitches were introduced the infected or at least inflamed, area was thereby made deeper, while important tissues were compressed and distorted.

While not certainly demonstrated in the thrombi near the operation wound, we believe that bacteria sure must be there. The fibrin was so dense (having taken the same stain as did the bacteria) that their definite identity was obscured.

\* \* \* \* \*

We have shown graphically what happens around a tonsillectomy wound. In a word, there are present hemorrhages, thrombi, necroses and bacteria. Hemorrhage causes rifts in the tissues, opens pathways for infection and destroys tissue. Trauma and disturbed blood supply result in necrosis. Injured bloodvessels are closed by coagula which may become infected and loosened.

Bacteria are carried into the tissues by physical force or are permitted to penetrate by the opening up of tissue clefts, especially when there has been some devitalization. These are present in an area which never can be put at rest, which constantly is open to reinfection and which is subjected to a great deal of constrictor muscle action.

What might be the consequences? Should a sterile thrombus be dislodged into the blood the result would be a small sterile pulmonary infarct which, however, later may become infected and give rise to pneumonia or an abscess. Should a septic thrombus be dislodged a lung abscess would be the probable result. Should a thrombus, either sterile or septic, reach a previously diseased area of the lung, such as a tuberculous focus, the lesion might be activated.

As yet there has been no postoperative study of tonsil cases in which the lungs have been carefully watched for small lesions. Lung infarctions after tonsil operations naturally would be small on account of the size of the peritonsillar veins, and it is perfectly possible that many a lung infarct caused by a non-septic embolus has escaped notice. *We would like to emphasize the following point:* One of the early signs of pulmonary infarction is the spitting of bright red blood, and it is quite possible that at times some of the blood-spitting in the early days following tonsillectomy is due to an overlooked infarction and not to oozing from the operation field. In our clinical work it might be well to keep this in mind and let this sign be a signal to examine the larynx and trachea as well as the tonsil fossæ, and also to have the chest examined and roentgen-rayed.

**Conclusions.** 1. The peritonsillar region as depicted in our specimens constitutes a postoperative field studded with thrombi, which may be either sterile or septic.

2. We believe that as trauma, sepsis and muscular action are the principal factors in the formation and dislodgment of thrombi, the actively muscular pharynx is a particularly favorable region for the dislodgment of such thrombi into the superior caval circulation.

3. We believe that many cases of pulmonary embolism escape notice on account of their small size, their sterile character and their prompt resolution.

4. It goes without saying that the performance of tonsil operations should be attended with every possible surgical device for promoting asepsis. We suggest, in the furtherance of this principle, that the routine use of needle-carried sutures for tying bleeding vessels be abolished and that surface ties be used instead.<sup>16</sup> The former are never surgically clean and we believe that their use carries with it possibilities of infection of at least the tissues adjacent to them,

5. While realizing that posttonsillectomy lung complications may at times be of inspiratory origin, we believe that such origin is not as common as has been thought.

6. While the infected condition of the lymphatic tissue found in our study must cause consideration to be given to a lymphatic origin for lung infections; we consider such origin to be rare.

7. Finally, it is possible that, in view of such studies as the present one, ideas in regard to the capsule of the tonsil may undergo a change. Instead of aiming to remove it, we may decide that it forms too good a bulwark to the peritonsillar tissues to allow of its being taken away. And we believe it to be entirely possible that some day the operation, called by Makuen<sup>17</sup> "intracapsular tonsillectomy," will be so demanded by the highest ideals of safety that in a perfected form it will be the operation performed by all of us.

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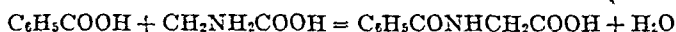
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## ODD CARBON FATS IN THE TREATMENT OF DIABETIC KETOSIS.

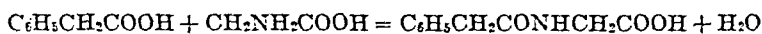
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It was shown by Knoop,<sup>1</sup> in 1905, that fatty acids in combination with aromatic radicals when given to animals are oxidized in a definite manner in the animal organism. It is known that if benzoic acid is administered by mouth it is excreted in the urine in conjunction with amino-acetic acid as hippuric acid, thus:



Phenylacetic acid is eliminated as phenaceturic acid:



If a higher acid than acetic acid is administered the resultant product eliminated is either the hippuric acid or the phenaceturic acid, depending upon the fact whether the side chain was of an odd or even number of carbon atoms. Knoop, therefore, concluded that in the oxidation of fats the  $\beta$ -carbon atom was oxidized and that two carbon atoms dropped from the chain together. This view was supported by Dakin's<sup>2</sup> discovery that when phenyl propionic acid was given in large amount phenyl  $\beta$ -oxypropionic acid was detected in the urine.

In this excellent summary on "Physiological Oxidations," Dakin<sup>3</sup> reviews the modern status of the theory of oxidation of fatty acids. I quote several of his paragraphs:

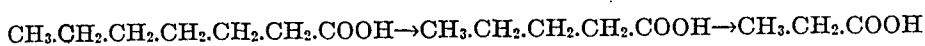
"In spite of a good many vigorous onslaughts, the theory of  $\beta$ -oxidation applied to fatty acids as put forward originally by Knoop has held its own. It will be recalled that one of the main supports of Knoop's views was furnished by Embden's observation that the normal fatty acids containing an even number of carbon atoms varying from 4 to 12 all gave rise to aceto-acetic acid when their salts were perfused through a surviving liver. The normal fatty acids containing an uneven number of carbon atoms failed to cause any increase in aceto-acetic acid production. An interesting clue to the probable fate of some of these normal fatty acids has been furnished by Ringer, who finds that propionic acid is practically quantitatively converted into glucose in the phloridzinized dog and that normal valeric and heptylic acids give an amount

<sup>1</sup> Hofmeister's Beiträge, 1905, 6, 150.

<sup>2</sup> Jour. Biol. Chem., 1909, 6, 203.

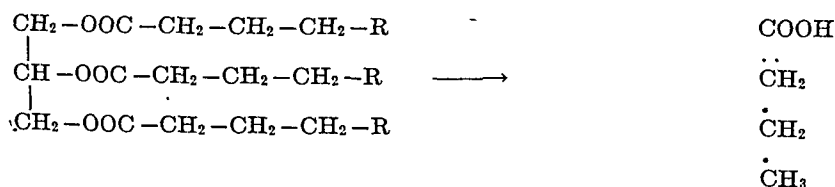
<sup>3</sup> Physiol. Rev., 1921, 1, 406.

of glucose under similar conditions comparable to the amount of propionic acid they might yield through  $\beta$ -oxidation:



"Blum and Woringer have recently shown that when propionic acid is given to normal dogs and rabbits, lactic and pyruvic acids are excreted, and these undoubtedly represent intermediary products of the oxidation of propionic acid, although it is not clear as to which of these two acids is first formed or whether perchance they are formed from acrylic acid, which Schwenken has shown to be almost quantitatively converted into glucose in the phloridzinized dog. The conversion of propionic acid into lactic acid explains the conversion of the former acid into glucose in the phloridzinized animal, for, as is well known, the conversion of lactic acid into glucose under these conditions is virtually quantitative. The formation of lactic and pyruvic acids from propionic acid must be regarded as a case of  $\alpha$ -oxidation, though possibly indirect, but since normal  $\beta$ -oxidation with formation of ketonic acid is no longer possible with a three-carbon acid it need not be regarded as violating the  $\beta$ -oxidation rule applicable to acids containing four or more carbon atoms. It appears, therefore, that in the metabolism of normal fatty acids containing four or more carbon atoms aceto-acetic acid is a common metabolite of all those with an even number of carbon atoms, while lactic acid is common to those with an uneven number."

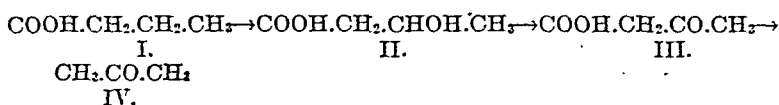
In the catabolism of fats (under normal conditions, that is, in the presence of proper carbohydrate oxidation) there is a rapid breakdown of the fatty acid radical to the four-carbon acid, *i. e.*, butyric acid:



The butyric acid is then rapidly catabolized to carbon dioxide and water.

This process is, however, markedly disturbed in states of deficient carbohydrate oxidation. In the latter circumstance the fats are primarily broken down to butyric acid, as in the normal condition, but in the absence of the heat of carbohydrate consumption the further decomposition of the butyric acid proceeds very slowly. The butyric acid under these conditions is decomposed first to  $\beta$ -oxybutyric acid and then to aceto-acetic (or diacetic) acid. The further decomposition to acetone takes place very largely in the urine itself.

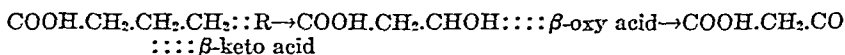




I . . . . .	Butyric acid.
II . . . . .	Beta-oxybutyric acid.
III . . . . .	Aceto-acetic acid.
IV . . . . .	Acetone.

Rosenfeld has said that fats burn only in the fires of carbohydrates, but this is not quite right, inasmuch as only the breakdown of the lowest products of fat decomposition, that is to say, the acetone substances, depends upon the catabolism of the carbohydrates.

How does the fat decompose to butyric acid? Of the two components of fat, only the fatty acids yield the ketone substances. The glycerin portion of the fat molecule is antiketogenic in nature. "By investigations performed either with living beings in a state of acidosis or with the transfused dog's liver, it has been established that fatty acids are broken down by a repeated splitting off of two carbon atoms. The first step is the formation of the  $\beta$ -oxy acid, which is then transformed to the  $\beta$ -keto acid:



The transformation requires a two-fold oxidation at the  $\beta$ -carbon-atom. Contrary to what happens in the lungs with aceto-acetic acid, a splitting off of the carboxyl group and the formation of true ketone generally does not take place in the metabolism; instead we find a simultaneous splitting off of the carboxyl group and of the  $\alpha$ -carbon atoms, thus yielding a new fatty acid lower by two carbon atoms." (Magnus-Levy.)

Embsen has found that only fatty acids of an even number of carbon atoms will yield aceto-acetic acid in the transfused dog's liver. In this way from stearic acid ( $\text{C}_{18}$ ), palmitic acid ( $\text{C}_{16}$ ) is formed; from this an acid with 14, 12, 10 or 8 carbon atoms is derived. Then caproic acid ( $\text{C}_6$ ) and, finally, butyric and oxybutyric acids are formed. The relative figures are as follows:

	Molecular weight.	Relation of molecular weight.	Per cent yield of oxybutyric acid from 100 gm.
$\text{C}_{18}$ . . . . .	284	100.0	36.5
$\text{C}_{16}$ . . . . .	256	90.0	40.0
$\text{C}_{14}$ . . . . .	228	80.0	46.0
$\text{C}_{12}$ . . . . .	200	70.5	52.0
$\text{C}_{10}$ . . . . .	172	61.0	60.0
$\text{C}_8$ . . . . .	144	51.0	72.0
$\text{C}_6$ . . . . .	116	41.0	90.0
$\text{C}_4$ . . . . .	88	31.0	118.0
<hr/>			
Oxybutyric acid, 104		36.5	

Several years ago<sup>4</sup> I endeavored to see the effect of the feeding of a fat containing an odd carbon fatty acid.

We have succeeded in preparing an odd carbon fatty acid fat that is edible, is absorbed to the extent of about 90 per cent, is catabolized in the body and does not yield the ketone substances derived from butyric acid.

The methods of preparation is as follows:

Stearic acid has its acid group substituted by an organic radical and upon oxidation with a strong oxidizing mixture the  $C_{17}$  acid ( $C_{16}H_{33}COOH$ , margaric acid) is produced. This is easily purified and then united with glycerol to form a neutral fat.

This fat, when well prepared, is of a white creamy color, odorless and tasteless, melting at  $38^{\circ}$  C. and neutral in reaction. When cold and granulated it is quite palatable. It does not cause any sense of nausea, and it seems to satisfy the hungry craving for fat that diabetics have. A number of patients were fed the fat, but it will be sufficient to describe 3 cases as the results are typical.

EXPERIMENT I.—It was thought advisable to induce ketosis in a normal individual and then see the effect of our fat on this ketosis. Accordingly, we advertised in the newspapers for a normal man willing to submit himself to a fasting experiment. From the many applicants, we chose A. A., aged twenty-three years, white, born in Sweden, who was by trade a cement worker and oftentimes a prizefighter. He was 5 feet 10 inches tall and weighed 144 pounds. He was in perfect physical condition. He undertook this task for the money that he was to receive.

He was placed in a separate room, with a male nurse in attendance. No food was given him whatsoever. Water was permitted as much as he wanted. He was fasted for seventy-four hours. His urine at the end of that time had marked quantities of diacetic acid and acetone. He was now given 100 gm. of our fat mixed with 100 gm. seven-times boiled string beans. Next day the urine was clear of acetone and diacetic acid. He was now given 100 gm. butter in 100 gm. seven-times boiled string beans. The urine next day showed again the ketone substances. During this day he received 200 gm. of the odd carbon fat in string beans and again his ketosis cleared up.

He was then discharged. His feces was analyzed (Dr. H. O. N.) and was found to contain 5 per cent of the ingested fat. The rest had been absorbed.

The subject did not complain of nausea or of any distaste for the fat. On the contrary, the butter was more distasteful to him than was our fat.

<sup>4</sup> About ten years ago Ringer suggested the use of such a fat. He was, however, unable to prepare one. Mosenthal also wrote of the desirability of such a fat.

The accompanying table shows the results obtained.

DATA ON FASTING EXPERIMENT.

Date.	Urine.					Blood.				Alv. air, Fredericia.	Remarks.
	Vol., cc.	Sp. gr.	Acetone.	Diacid.	NH <sub>3</sub> , gm.	CO <sub>2</sub> , per cent.	Urea, N.	Creat., mg.	Glucose, per cent.		
June 12	....	1.021	○	○	....	50	20.4	1.25	0.1	5.4	Began fast 1 P.M.
June 13	640	1.030	○	○	0.75	..	....	....	....	5.2	Fasting.
June 14	1460	1.016	○	○	1.38	..	....	....	....	4.8	Fasting.
June 15	1350	1.018	++	++	3.25	37	....	....	0.08	4.0	3 P.M. received 100 grams Intarvin and 100 grams 7x washed string beans.
June 16	1480	1.014	○	○	1.45	45	....	....	0.08	4.6	1 P.M. received 100 grams butter and 100 grams 7x washed string beans.
June 17	1220	1.016	++	+	3.80	37	....	....	0.08	4.1	Received during day 200 grams Intarvin and 100 grams 7x washed string beans.
June 18	1430	1.018	○	○	2.75	48	15.7	2.25	0.06	4.8	

EXPERIMENT II.—A diabetic woman (A. S.), aged forty-seven years, was admitted to the gynecological service with the diagnosis of tumor of the adnexa. She had been under my care previously for a year. She had lost much weight and was in a condition of acidosis and hyperglycemia and glycosuria when admitted to the hospital. I urged the surgeon to wait with the operation until we could render her non-ketotic, but this was found to be impossible at the end of ten days, although she was kept on a diet fat-free as possible. She was catabolizing her body fat and her urine was heavy with diacetic acid and acetone.

## A. S.

Date.	Food, gm.				Urine.		Blood.		
	P.	CH.	F.	Odd fat.	Glucose.	Diacid.	Acetone.	CO <sub>2</sub> , per cent.	Glucose.
Nov. 29, 1921	..	..	..	..	....	....	....	44	0.25
Nov. 30, 1921	39	16	22	0	40.9	+++	+++		
Dec. 1, 1921	31	19	17	0	32.6	+++	+++	42	0.23
Dec. 3, 1921	42	15	8	0	27.9	++++	+++		
Dec. 6, 1921	60	15	4	0	31.4	++++	+++	44	0.22
Dec. 7, 1921	45	15	4	90	....	○	+++		
Dec. 8, 1921	45	15	4	90	Trace	○	○	56	0.17

To the same fat-free diet we added a daily ration of our fat of 3 ounces. The patient, it seemed, aridly absorbed this fat and in forty-eight hours the urine was free from diacetic acid. This case was rather puzzling to us, for not only did her ketosis cease, but her glycosuria was markedly diminished.

The cause of ketosis, the most common form of which is the acidosis of diabetes, is a disturbance in the catabolism of the fats induced by either starvation, infantile malnutrition or anesthesia induced by lipin solvent anesthetics besides diabetes. We have studied the ketosis of diabetes and starvation and it is expected in the near future that tests on the other types of ketosis will be carried out.

EXPERIMENT III.—A. S., male, aged forty-four years, married, with two children. For the past five years the patient has had diabetes. One year and a half ago he weighed 185 pounds. He was then removed to a sanitarium and put on the undernutrition treatment so that he lost 110 pounds. For the past several months he has been in bed suffering from general furunculosis, cachexia and pulmonary tuberculosis. He was unable to get out of bed, attend to himself and so on.

In order to keep him sugar-free and ketone-free he was kept on a diet of about 500 calories daily, with a fat intake of 34 gm. and a carbohydrate intake of 8 gm.

The patient was brought to the hospital in this very serious condition. The addition of several grams of fat to the diet in the form of butter or egg-yolk immediately brought about an acetone reaction in the urine.

We, therefore, placed the patient on a diet of protein, 38 gm., carbohydrate, 8 gm., and fat, 34 gm. In addition to this we gave him daily 150 gm. of the "odd carbon" fat, thus increasing his caloric intake from about 500 calories daily to about 1700 calories.

He relished the fat. His hunger was allayed. During a period of ten weeks he gained 10 pounds in weight. His urine remained free from sugar (except for faint traces on three days during a period of nearly four months). His fat catabolism was normal; no acetone nor diacetic acid appeared in his urine. His carbon-dioxide combining power of the blood plasma was normal.

His tuberculosis, however, was not improved. It became necessary to send him to a hospital for the care of tuberculosis because of his expectoration and cough. Several weeks after his transfer he died from a pulmonary hemorrhage.

The data that are of interest in this case are presented in the accompanying table. It was observed that the addition of any normal fat, either inadvertently or purposely, resulted in the appearance of the ketone substance in the urine.

A. S.

Date.	Food.				Urine.		Blood.	
	P.	C.	F.	Odd fat.	Glucose, per cent.	Ketones.	Glucose.	CO <sub>2</sub> .
Feb. 20 . . .	40	20	42	0	Traces	++	0.224	44
Feb. 22 . . .	40	35	40	...	1.4	++	0.227	46
Feb. 24 . . .	37	13	31	0	0	○	0.185	48
Mar. 2 . . .	40	20	42	0	Traces	++	0.195	42
Mar. 6 . . .	37	13	31	0	0	○	0.175	48
Mar. 10 . . .	42	15	37	0	0	○	0.162	48
Mar. 14 . . .	42	15	37	100	0	○	0.151	54
Mar. 20 . . .	42	15	37	100	0	○	0.148	54
May 24 . . .	42	15	37	150	0	○	0.113	58
June 8 . . .	44	17	37	150	0	○	0.134	58

EXPERIMENT IV.—R. G., aged twenty-five years, was suffering from pituitary glycosuria with marked emaciation and loss of weight. She weighed 75 pounds and showed distinct evidence of ketone substances in the urine. Upon feeding of the odd carbon fat the acetone cleared up and during a period of several months she gained 10 pounds in weight. It is worthy of note in this case that the administration of insulin had absolutely no effect on the presence of the glycosuria or in the control of the loss of weight.

The accompanying table shows some of the figures obtained.

R. G.

Date.	Food.				Urine.		Blood.	
	P.	C.	F.	Odd fat.	Glucose.	Ketones.	CO <sub>2</sub> .	Glucose.
Feb. 9, 1922	62	36	90	0	3.2	++++	48	0.23
Feb. 11, 1922	60	20	68	0	1.7	+++	..	0.24
Feb. 12, 1922	57	16	20	90	0.6	++	..	0.21
Feb. 13, 1922	60	12	18	90	○	○	58	0.16
Feb. 15, 1922	62	17	40	0	+	+++		
Mar. 4, 1922	60	18	15	100	+	○	56	0.17

The fat is administered by mouth in the following ways: (1) Granulation of the fat and direct consumption with the aid of salt, pepper or vegetables; (2) baking with the fat: it was used in the preparation of Lister's bread, etc.; (3) frying with the fat after "rendering" it with onions; (4) in the form of an ice-cold emulsion in buttermilk, etc.; (5) in the form of a flavored drink; (6) with hot drinks, such as coffee, broth, etc.

**Summary.** 1. Ketosis is due to the pathobolic breakdown of fats in the absence of carbohydrate oxidation.

2. Natural fats are all glycerides of fatty acids containing an even number of carbon atoms, which during abnormal breakdown yield butyric acid and the ketone substances of diabetic ketosis.

3. An odd carbon fatty acid fat has been synthesized which is palatable, is absorbed to about 90 per cent and is catabolized in the body of diabetic patients without the production of ketones.

4. The diabetic patient's diet can be much increased by this fat. It allays hunger and stops the loss of weight.

5. It may be fed *ad libitum*.

## FURTHER OBSERVATIONS ON ARTHRITIS AND RHEUMATOID CONDITIONS.

BY RALPH PEMBERTON, M.D.,

PHILADELPHIA.

ABOUT three years ago the writer published an article,<sup>1</sup> based somewhat upon researches conducted on a large scale in the army,<sup>2</sup> in which the attempt was made to correlate into a whole, some of the demonstrated and suggested facts regarding the problem of arthritis, with the aim of visualizing at least part of the pathology of arthritic and rheumatoid conditions. Since then, further data and viewpoints have been arrived at sufficient to justify a recapitulation: This is attempted in the present contribution.

In the study of large subjects like arthritis, diabetes, arteriosclerosis and metabolic disturbances in general, it is obvious that the solution is rarely to be expected from a single experimental *coup de grâce*. The situation differs from that presenting in certain purely bacteriological or parasitic diseases where the discovery of a causative organism may largely clear up the field. While it is known, for example, that many cases of arthritis are precipitated by streptococci and other organisms, acting through so-called focal infections, other cases are apparently precipitated by different factors and in any event the mechanism concerned in the production of the symptoms and lesions has remained entirely obscure.

The true conception of diseases such as those mentioned must come from the piecing together of a host of data in many fields, chiefly physiological in nature. It is probable that for some time at least, anything like a full understanding of these conditions, based solely upon exact data, will be beyond our power and it becomes therefore appropriate and necessary to make such reviews of the field from time to time as new and changing data permit.

In the articles above mentioned, attention was directed to the several reasons for regarding arthritis and rheumatoid conditions

as referable to some disturbance in certain phases of the local or systemic oxidative metabolism, possibly involving the circulating blood. Since then, observations have been conducted in a number of directions which have given a somewhat different slant to the course of experimental work without changing its basal nature and purposes.

By way of résumé, it may be mentioned that the studies in the army above referred to showed normal values for nitrogen, calcium and fats in the fasting blood, a slight lag in the elimination of salt and water, a slightly lowered basal metabolism in 20 per cent of the cases studied and a definitely lowered sugar tolerance. This lowered sugar tolerance was most marked in general in the worst cases of arthritis, was definitely improved in convalescent groups and could be seen to return toward normal in many individual cases as they convalesced and recovered. This return to normal was independent of the type of successful therapy employed, but was most abrupt after the removal of causative infections. The lowered sugar tolerance was uninfluenced by such agents as the salicylates even in the presence of symptomatic improvement.

Observations recently reported<sup>3</sup> show that under the given conditions of the experiment, making brief use of a tourniquet, it was not infrequently possible to demonstrate a difference in the percentage oxygen saturation of the peripheral venous blood of arthritics as compared with normal persons. In some cases this difference, which consists in higher figures for the arthritics, was found to be very marked. It seemed at times to lessen with convalescence from the active process.

It was also shown that during the demonstration of a lowered sugar tolerance in arthritics, by the usual technic, there occurred a rise in the per cent saturation of the blood, which paralleled the arthritis rather closely, though absent in normal persons giving a normal sugar tolerance. The percentage saturation of oxygen very definitely rose even in some cases of arthritis with a normal sugar tolerance, so that in this respect also arthritics seemed to differ from normal individuals. Indeed, they could be grouped somewhat by this analysis alone without ascertaining the sugar figures. Experiments have shown, however, that the mechanism by which the respective concentrations of oxygen and sugar were brought about, are apparently different.<sup>4</sup>

While these general results were in keeping with the hypothesis on which these studies were based, attempts to relate them to chemical changes in the composition of the blood were not altogether successful; in fact, study of the blood gases in respect to the so-called dissociation curves for oxygen and carbon dioxide gave normal values and it became necessary to look in some other direction for the explanation.

As the result of certain recognized changes in the gaseous equilibria

of blood coming from a hyperemic part, and as the result of observations by Pemberton, Hendrix and Crouter<sup>3</sup> in collaboration with R. B. Osgood, that the percentage oxygen saturation rises markedly during an electric "bake" of the whole body it was believed that some solution might be found on the basis of changes in the rate of circulation. Experiments were therefore conducted by means of Stewart's hand calorimeters upon the rate of blood flow in arthritics and normal persons. While the results of these studies do not permit as yet of final conclusions, additional impetus was given to the view that the blood flow in arthritis, in the capillary circulation especially, may be below normal. Without citing here the evidence which makes up this view (*loc. cit.*), suffice it that this viewpoint lends itself to an explanation of a number of obscure factors in arthritis and also paves the way for further hypothesis.

It is of much interest for example, to note that the joints are structures whose blood supply is very small. Attention has been drawn to this in a previous communication.<sup>1</sup> The insertion of tendons, another favorite spot for arthritic disability, is also a point of poor blood supply. Furthermore, other structures whose blood supply depends upon extremely small bloodvessels are characteristically involved at times in arthritis, for example, in the painful condition known as irido-cyclitis. The frequency with which psoriasis may accompany arthritis is well known and here again it is noteworthy that the capillaries and nerve endings do not penetrate to the outer layer of the epidermis which is the chief seat of the lesion.<sup>5</sup>

By extending these considerations a little further it is of interest to note that in the muscles which constitute one of the chief sites of rheumatic disability, conditions are rather delicately balanced for the proper gas interchanges. Thus in tissues, such as the submaxillary glands, the tissue oxygen pressures approximate the venous oxygen pressure whereas in some others, including skeletal muscle, the oxygen pressure in the muscle is 25 mm. or less, *i. e.*, much below the capillary oxygen pressure. In the former, therefore the blood flow can be diminished to a considerable degree<sup>6</sup> without loss of oxygen to the tissue, but in the latter it cannot. In the same connection Krogh has shown<sup>7</sup> that the oxygen pressure in resting muscles is sometimes at least very low, but in working muscles it approximates that of the blood. Reference will be made later to the significance of these facts.

Some interesting collateral information can be adduced from the results of the expedition of Barcroft and his collaborators to the Andes for the purpose of studying the respiratory functions of the blood at great altitudes.<sup>8</sup> They observed among other points, that the condition of sore muscles popularly known as "charley horse," which arises more easily in the arthritic than in normals, followed



a smaller amount of exercise than is the case at low levels and they also noted that acclimatization was frequently accompanied by an enlargement of the ends of the fingers suggesting the condition known as hypertrophic pulmonary osteoarthropathy. It is well recognized that in certain forms of this condition the bony structure itself is increased.

Further study of the gaseous interchange under conditions known to benefit the arthritic process has opened other viewpoints of interest. Thus, Bazett and Haldane<sup>9</sup> have shown that normal subjects, immersed to the neck in a bath at 38° C. experience a rise in body temperature accompanied by hyperpnea, giddiness and faintness; they also noted a fall in the alveolar carbon dioxide a profuse alkaline sweat and a marked alkaline diuresis. This alkaline wave they compare to the changes occurring after voluntary forced breathing. Haggard has observed a drop in alveolar carbon dioxide with the increased temperature in a normal person immersed for twenty minutes in a bath at 40° C.<sup>10</sup> He observed a fall in the dissolved carbon dioxide but no change in the carbon-dioxide combining power of the blood, and deduces that the concentration of hydrogen ion (PH) of the blood must be presumably lowered. Pemberton, Hendrix and Crouter have observed<sup>3</sup> a similar fall in alveolar carbon dioxide in normal and arthritic persons subjected to "electric bakes;" and also a rise above normal in alveolar carbon dioxide after the bake in nearly every instance.

Studies of the sweat resulting from external heat or other stimuli have been conducted by very few workers and have given varying results, but the writer in collaboration with C. Y. Crouter<sup>4</sup> has observed the interesting fact that the sweat of the forehead of arthritics may occasionally reach a lower PH., (around 4.6) that is a greater acidity, than that of normal persons, and the further interesting fact that with both normals and arthritics there is a nearly invariable tendency for the sweat to become less acid or more alkaline as the "bake" or application of heat progresses. The only exceptions to this have been some cases of arthritis and one of scleroderma which remained acid throughout, at figures rather more extreme than any normals reached.

These facts can be correlated with the few known facts relating to the elimination of CO<sub>2</sub> through the sweat. According to Riffle *et al.*, excretion of acid is a function of skin and kidney<sup>11</sup> and according to Starling<sup>12</sup> at a temperature of 29° to 33° C., CO<sub>2</sub> output increases so that at 34° it is doubled and at 38.5° it may amount to as much as 1.2 gm. per hour (Schierbeck).

Recent studies by Cajori, Crouter and Pemberton have shown that if a rubber bag be placed around an arm during a general body bake the carbon-dioxide content of the bag rises parallel with the drop in the reaction of the sweat of the forehead or other

arm. The same workers\* have also shown that there is an actual decrease in the hydrogen-ion concentration of the blood; that is, the blood becomes more alkaline as shown by the  $\text{CO}_2$  absorption curves and by direct measurement of the  $\text{PH}$  by Cullen's method. In one case, the change was from a  $\text{PH}$  of 7.26 to 7.52. Koehler† has obtained similar results. The evidence is all in favor of the view that this change results from a loss of acid from the body, presumably  $\text{CO}_2$  in part; somewhat through the sweat but more largely through the lungs and urine. The probability that the elimination of  $\text{CO}_2$  plays a role in the benefit accruing from "bakes" has been suggested by Pemberton, Hendrix and Crouter<sup>3</sup> and unpublished work of Cajori, Crouter and Pemberton indicates that other acid substances are also eliminated through the sweat.<sup>13</sup>

It is obvious that some of the benefits of hot packs and sweats in conditions accompanied by an acidosis, such as nephritis, is referable to the loss of acid and to the alkalosis induced.

An important corollary can be drawn here as to the common denominator between the beneficial effects of external heat in arthritis and the benefits following exercise, and to a lesser degree massage. The periods of greatest malaise of the arthritic are following rest (sleep) in the early morning hours (4 to 5 A.M.), at which time the body temperature is lowest. The clinical state of the patient generally improves as the day wears on and toward 6 to 7 P.M. opposite conditions prevail, accompanied by parallel oscillations of the metabolic rate as shown by the elimination of carbon dioxide. Exercise in general is of benefit to rheumatoid conditions and is accompanied by a complex train of events which cannot be detailed here. The increased ventilation of  $\text{CO}_2$  and the increased blood flow which accompany it, however, are probably analogous to those resulting from bakes. It is important to note that the transport of  $\text{CO}_2$  is effected mainly by the cells, probably by the hemoglobin.<sup>14</sup> The content of blood  $\text{CO}_2$  also depends largely upon its production in the body and this fact is to be borne in mind when considering later the beneficial consequences of low caloric diets.

It is well recognized that among the chief symptoms of arthritis are the absorption and deposition of bony tissue, which constitute an expression in the osseous structures of a process which operates in many other and possibly all tissues. There is not a little precise data available here. The suggestive work of Allison and Brooks,<sup>15</sup> has shown in dogs that non-use through nerve section may bring about a loss of more than 25 per cent of the mineral constituents of the bones in twenty-four days, due to a loss of the bone matrix rather than to a change in its composition. The condition induced is obviously one of metabolic inactivity, and, by the same token,

\* Jour. Bio. Chem., 1923, 57, 217.

† Arch. Int. Med., 1923, 31, 590,

Lipschutz and Audova,<sup>16</sup> have reached the conclusion that atrophy of muscle following section of tendon may be nearly as great as that following section of the nerve supply and that the inactivity which follows, plays a decisive part in determining the atrophy. In line with these observations is the evidence that normal ossification and pathological calcification depend upon physico-chemical factors and variations in  $\text{CO}_2$  concentration.<sup>17</sup> It would appear that bony overgrowth does not essentially differ from normal bone and it is logical therefore to regard most forms of rarefaction and deposition as the result of changes in the intensity of local metabolic processes rather than of the introduction of new mechanisms. It is to be recognized of course that the various normal factors concerned may also vary in their relation one to another.

There are in the above experimentally ascertained facts ample data with which to attempt explanation of the mechanism producing the bony changes in arthritis. The evidence is at least suggestive that something interferes with the utilization of oxygen or its removal from the peripheral blood and on the basis of the premises already outlined the most likely explanation at present lies in some disturbance of the capillary or finer vascular control. The result is comparable to some of the effects produced at altitudes under conditions of anoxemia. Thus Schneider and Gregg and others have directed attention to the frequency, under such conditions, of fatigue and headache which are among the most frequent concomitants of the rheumatic syndrome. The interesting observations of Barcroft *et al.*, on muscle fatigue and stiffness have already been cited. Until evidence to the contrary is forthcoming, one can believe that absorption and deposition of bony tissue are partly functions of changes in the gas equilibria at the part concerned. There might be little or no systemic evidence, in terms of changes in the end-metabolism, from such minute disturbances in the gas equilibria. These would be restored to normal when the blood from the part had passed beyond the zone of involvement to the more actively circulating current. It is at all events clear that we are dealing here with true chemical processes and analysis shows that the radicals of  $\text{CO}_2$  and  $\text{P}_2\text{O}_5$  play much of their usual important role in the bony metabolism.

It is indeed not necessary to postulate the presence of products of anoxemia such as the  $\alpha$ -hydroxy acids although these may also be present. The formation of acids at the anoxemic centers of big infarcts during autolysis together with their neutralization at the periphery by the blood plasma have long since been recognized as established processes.<sup>18</sup> It is of the highest importance to note that, in contrast with the circulating blood, the fixed tissues cannot make use of the regulation of  $\text{CO}_2$  content by pulmonary ventilation. Such fluids as the synovial are similarly handicapped because of the absence of cells and it has been shown that lymph becomes acid more readily than does the blood, for the same reason.

The suggestive researches of Jacobs<sup>19</sup> on the toxic and penetrating qualities of CO<sub>2</sub> in plants, even in alkaline solution, form the basis of much interesting speculation and experiment along this line and deserve consideration in relation to animal physiology. For further development of the problem of local tissue acidosis, however, and the chemistry concerned the reader is referred to the work of Schade, Neukirk and Halpert.<sup>20</sup>

The influence of "focal infection," brought about frequently by the action of streptococci upon surrounding tissues, finds some acceptable explanation along these lines, in the researches of Hoover, Rich and others. As above mentioned these workers have demonstrated the effect on the capillary circulation of a variety of substances resulting from proteolysis of which histamine is a type. Some interesting recent work of Manwaring and Boyd has shown that the effect of some bacterial toxins upon the capillary endothelium of the perfused heart is to produce marked edema and hemorrhage of the myocardium, dilatation of the tissue spaces, and the extravasation of numerous red blood cells.<sup>21</sup>

As already remarked, the sum total of these processes, however, is usually small and it is probably for this reason that so little disturbance is observed in determinations of the end metabolism; Cecil, DuBois *et al.*<sup>22</sup> observed a normal metabolic rate and normal rate of utilization of ingested carbohydrate in a series of 4 arthritics studied by them. The writer in collaboration with E. H. Tompkins observed a slight reduction in the metabolism of 20 per cent of 29 arthritic soldiers studied in the army. Marked disturbance are necessary before they show themselves in summation figures and it is clear on many counts that we must learn to think in terms of local acidosis and local departures from normal metabolism. Putting aside such metabolic changes of a more or less well-known nature in the smaller structures, there are also many unknown links in the chain of intermediary metabolism, interruption of which might be unrecognizable in end metabolic figures.

It is possible that some of the proliferation of tissues such as the pannus which covers the joint cartilage in the "proliferative" form of arthritis of Nichols and Richardson is in part a compensatory phenomenon seeking to vascularize the affected region with the aim of supplying adequate nutrition. By the same token, it is conceivable that the formation of fibrous tissue so frequently seen in arthritis is an expression of the same principle and indeed, this thought may be further extended to include the formation of fibrous tissue in some widespread pathological processes.

In addition to the disturbances in the local chemistry at a given site, inaugurated in a more or less mechanical way by changes in the smaller vascular channels, it is obvious that alterations in the nature of the blood passing through these channels may further

profoundly modify the situation one way or another. Thus, anemia is a sequel of chronic arthritis which tends greatly to aggravate the disease process. The corollary of this, however, is fortunately of clinical value and some of the most marked improvements in arthritis occur during the period when a secondary anemia is yielding to the influence of such an agent as arsenic. The heightened nitrogenous interchange and increased metabolism which result, contribute to this end, but one factor seems clearly to be the regeneration of red cells and the increase in hemoglobin. Partial proof of this is seen in the fact that improvement frequently ceases when the blood count has been brought up to normal or nearly so. The writer has seen many instances of this.

Following this thought and anticipating somewhat consideration of the influence of climate, etc., it may be said that the subacute arthritic frequently experiences an abrupt and somewhat striking improvement in passing from low to moderately high altitudes. It is well recognized by physiologists that there are two forms of adaptation to high altitudes. In the former, there is an almost immediate increase in the red cell and hemoglobin count, which is limited in degree and duration. It may last many days, however, and it is believed that during this period there are brought into circulation many red cells which had been more or less out of the active circulation. In the latter form of adaptation on the other hand, there occurs after a more prolonged stay at altitude a more lasting increase in hemoglobin and red cells, which is a direct function of the degree of altitude and the duration of exposure to it. There is also a marked increase in the percentage of young red blood cells. It is of interest to observe that the arthritic may undergo an exacerbation of his symptoms if he be transported abruptly to considerable altitude, but after acclimatization the change in the blood count is accompanied by a return to his usual clinical condition and sometimes by a betterment in his symptoms which may last for some time after reaching lower levels.

There are some other features of the blood count which will bear mention at this point, although properly belonging under the question of diet which will be taken up later. The injection of non-specific protein and killed bacteria, which recently had quite a vogue, is apparently now regarded by Miller and by Snyder, (personal communications) who have probably had the largest experience with it, as of value chiefly in the acute or subacute cases and to a limited degree. Attention has been called in a previous article,<sup>2</sup> to the mechanism probably operative, but another factor to which benefit has been ascribed is the increase in polymorphonuclear cells. In contrast to this, the improvement which follows the institution of a low caloric diet in suitable cases is generally accompanied by a more or less pronounced relative lymphocytosis. That this increase is the concomitant of a low diet *per se*, is further

indicated by the studies of Benedict<sup>23</sup> who showed that among a squad of men living upon 1950 calories, the leukocytes remained normal but the lymphocytes were increased. There is definite evidence in this that improvement is not incompatible with an increase in the percentage of lymphocytes without change in the polymorphonuclears. It also militates against the view that the increase in polymorphonuclears is the prime factor in the benefit which occasionally follows non-specific protein therapy. It may be remarked that the increase in the blood count at moderately high altitudes which is sometimes accompanied by improvement in the arthritic process apparently chiefly or solely concerns the red cells and hemoglobin.

Attention has been called in previous publications<sup>24</sup> to the unquestionable benefits which follow the use of a restricted dietary in appropriate cases. These findings have recently been corroborated on a large scale by Fletcher<sup>25</sup> and also by others.

Perhaps one of the most useful purposes served by this form of treatment has been to afford a different visual angle and therefore another approach to the problem of arthritis. It has been pointed out elsewhere<sup>1</sup> that there must be recognized in arthritis two distinct groups of factors having influence, namely, the causative factors of exposure, various kinds of infection, intestinal malfunction, etc., relief of which may or may not cure the disease, and second, the various agents, such as heat, arsenic, radium, exercise, massage, sweats, etc., which have a distinct influence on the local or systemic metabolism. These last may operate even in the presence of the causative factor, they are quite independent of it, they produce their results in somewhat differing ways and they indubitably reflect part of the pathology concerned.

In line with the thought advanced earlier in this paper, it is important to note that nearly all measures of benefit *per se* in arthritis and rheumatism depend upon an increased local or systemic metabolism or upon an increased local or systemic blood flow. Demonstration of the influence of external physical stimuli upon the capillary circulation as shown by the studies of Krogh *et al.*, is of great assistance in enabling us better to understand the *rationale* of such measures as massage and external heat. The work of Carrier in this connection is particularly pertinent.<sup>25</sup> These considerations also add weight to the view here suggested that at least part of the pathology of arthritis is referable to disturbance in the finer vascular mechanism and blood flow.

It can be said with reasonable probability, however, that when a low calory diet proves of benefit, it does so on one hand by virtue of a reduction of some of the products of intestinal malfunction, causative of certain types of arthritis, and on the other hand by virtue of the lowered metabolic burden to be borne either in a systemic sense or locally at different sites. A lowering or adjust-

ment of this metabolic burden is the natural corollary of measures to hasten and improve the metabolic processes concerned, and often has brilliant results. As far as this phase of the question is concerned dietetic therapy has much of the limitation of any method which caters to a weakened function and should be used with a balanced appreciation of both sides of the equation.

In some recent studies by Pemberton and Crouter<sup>4</sup> observations were conducted upon the hydrogen-ion concentration of the feces in a number of cases of normal individuals and arthritics, the latter of whom included cases convalescing upon dietary lines. The hydrogen-ion concentration, however, ran very consistently between 6.4 and 7.4 for all classes of cases, and it could not be determined that subjects convalescing upon a diet gave figures different from those still ill or from normal subjects. So far therefore as the reaction of the feces can reflect the reaction of the intestinal tract, the evidence is against the view that changes in the hydrogen-ion concentration following reduction in the diet, chiefly of carbohydrate, constitute the factors of value.

Another interesting point in connection with the influence of diet is to be found in the betterment which some subjects experience, when eating an unrestricted diet, immediately following the ingestion of food. This effect is most marked in the early morning hours, their worst period. It has been shown that an immediate influence of food is markedly to increase the rate of blood flow in at least the peripheral circulation and Pemberton, Hendrix and Crouter<sup>3</sup> have shown that this influence is well marked in arthritis. Not only the arthritic disability *per se* but also muscular stiffness and the systemic fatigue and mental habitude of the arthritic may be markedly the momentarily influenced for the better. Thus the effect of coffee in the morning is sometimes temporarily striking as many arthritics can testify.

It is important to stress again the point previously mentioned<sup>1</sup> that after the inauguration of arthritis from such causes as focal infection or prolonged exposure there may occur a more or less chronic dislocation of physiology such that removal of the cause in late cases is no longer adequate to bring about recovery. In such instances other factors, within the economy, which would be at other times harmless, may operate to perpetuate the condition already outlined. Some of the "intestinal" forms of arthritis apparently rise *sui generis* but it seems probably that some of them also arise in the manner just mentioned, and appreciation of the train of factors concerned is sometimes necessary before important improvement can occur. It is pertinent to call attention here to the suggestive work of Bodine,<sup>27</sup> of Child<sup>28</sup> and of Hyman<sup>29</sup> who have shown in general that in certain lower forms of life the influence of fasting tends toward an increase of metabolism per kilogram and a rejuvenescence as regards the rate of oxidation.

The infrequency of arthritis or rheumatism in the course of severe diabetes has already been mentioned.<sup>1</sup> Since then, the courtesy of a few colleagues at scattered points and in medical audiences has called to the writers' attention a few cases in which the two processes were combined in mild degree, but instances of active and sustained arthritis in the course of severe diabetes are yet to be encountered. Information bearing upon any such cases would be appreciated by the writer.

One of the most interesting consequences of the application of the above hypothesis to the problem of arthritic disability is the explanation which is afforded of the influence of climate and weather upon the disease. Perhaps nothing is more firmly ingrained in the mind of the profession, as well as the laity, than that rheumatic symptoms sometimes undergo exacerbation and amelioration more or less coincident with certain outstanding changes in the weather. The writer has for some years kept a series of charts in which the attempt has been made to correlate these changes in the clinical condition of patients with fluctuations in the temperature, humidity, barometer and certain other factors. Observations are still pending but it can be said that there seems to be no constant single factor accompanying these changes. Increased humidity, a rising thermometer, a marked fall in the barometric pressure may all have their influence. It has long been taught in text-books that the metabolic rate in man remains practically constant because of the environment created by his clothing. It has been shown, however, that the metabolism of men at work in Africa is 10 per cent less than that of the same men at work in Berlin.<sup>30</sup> Furthermore, Ash and Hill<sup>31</sup> found that cool out-of-door conditions raise the basal metabolism even in the absence of shivering. It seems probable that the distinct exacerbations of arthritis which may accompany a rise in temperature are partly due to the tendency toward less intense metabolism. There is another factor which operates here, however, and that is the vapor tension which increases with the rise in temperature. It is of interest to note in this connection that there is a distinct vernal increase in the incidence of arthritic conditions. The writer has observed this for some eight years or more and Lambert<sup>32</sup> has also called attention to it in his analysis of the records of Bellevue Hospital, New York. Study of the records of the U. S. Weather Bureau<sup>33</sup> brings out the fact that the only discoverable constant operating in nearly all parts of the country, aside from the rise in temperature, is the so-called "march of the vapor tension" which begins in February and reaches its highest value in summer (July), corresponding almost precisely to the period of increased rheumatoid disability as viewed by long range perspective. The significance of this factor in its entirety remains to be worked out, though certain probable effects are obvious. Part of the benefit from moderate altitude may arise from the lower vapor pressure obtaining there.



On the basis of the pathology outlined, it is obvious also that the effect, upon a part, of exposure, following lying on cold stone or exposure of a wet surface to wind, finds explanation in the local circulatory changes which ensue. Finally, if the role of the circulation is postulated through either its vascular control or chemical make-up, it follows that changes in the barometric pressure probably have influence pro or con in the performance of the respiratory functions and in certain other respects. The influence of the weather on metabolism is further to be seen in the interesting figures arrived at by Murlin and his co-workers.<sup>34</sup> They observed that the winter ration of the U. S. troops in France contained over 5000 calories per man daily and that the total daily consumption of food per man averaged 3633 calories. Each man required approximately 400 more calories daily during the period October to March than during the remainder of the year. The period of lessened requirement and hence presumably of lessened metabolism corresponds almost exactly with the increased incidence of arthritis as above noted.

Theoretical considerations suggest and practical experience has shown that the climatological conditions best suited to the arthritic are those characterized by a reasonable degree of altitude of a thousand feet or so, a dry soil and a dry atmosphere. The benefits accrue chiefly after a visit to such regions and it is not to be supposed that people living under such circumstances are necessarily free from arthritis; indeed, the writer has had several patients from Arizona whose trouble originated in regions where the above conditions obtained and where the subjects had lived for years. In borderland cases, however, and those "hanging fire" the influence from these factors may have large importance.

For some years the Boston school of Orthopedists, particularly Goldthwaite, Osgood and their co-workers have advocated with success in certain types of cases, postural and active exercises of various sorts. It is obvious that any defect in the circulatory conditions as above outlined would be aggravated by relative stasis of the blood stream elsewhere or by protracted congestion of the viscera from malfunction, malposition or ptosis and it seems probable that at least part of the benefit accruing from these valuable measures finds its explanation here. The hyper-ventilation recommended probably also finds part of its justification along these lines.

There are many other facts in relation to the problem of arthritis and rheumatoid disabilities which allow of extending the usual visual angle and also afford leads for investigative attack. Space will not permit, however, of mentioning them here.

It was stated at the outset that no suggestion of finality was to be attributed to the outline of the pathology of arthritis herewith presented. The basis for this outline is to be found in many

established facts and in many suggested facts some of which are now the subject of investigation. It is obvious that as further studies substantiate or disprove the various tentative conclusions reached, any hypothesis seeking to visualize the subject as a whole will be subject to such modifications as are necessary in the attempted solution of any complex problem. It is hoped to make such studies and modifications the subject of later contributions.

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## THE OCCURRENCE OF FEVER IN MALIGNANT DISEASE.

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FEVER as a symptom of malignant disease has long been recognized and in fact occupied a prominent place in the writings of a generation ago. Frequent mention was made and considerable emphasis laid on fever in abdominal neoplasms by writers in the eighties and nineties but in later years this symptom has receded into the background, overshadowed, like many another purely clinical observation by the more spectacular findings of the laboratory. That a prolonged and marked hyperpyrexia can exist with uncomplicated cancer is a possibility that well nigh has been forgotten by medical men of today. As proof of this, witness the fact that in two of the most popular and recent systems of medicine no mention is made of fever occurring with cancer of the stomach. The further back one goes in the text-books and literature the more is reference to this point found.

The most comprehensive article is the statistical one of Max Freudweiler<sup>1</sup> embracing 475 carcinoma cases in the Zürich Clinic from 1884 to 1897. Over one-half these cancers were gastric and all but 40 were in the digestive tract. The occurrence of fever in all uncomplicated cases was 24.6 per cent and varied from 45 per cent of the liver and gall-bladder cases to 21 per cent of the pharynx and esophagus.

Naturally most of the statistical work has been done on carcinoma of the stomach. Osler and McCrae<sup>2</sup> in their clinical study of 150 cases of cancer of the stomach give fever as occurring in 49 per cent and Friedenwald<sup>3</sup> in a similar study found 43 per cent febrile. In 18 per cent of these febrile cases of Friedenwald's the fever ran through the entire course of the disease, in 25 per cent it occurred during the first six months, and in 74 per cent the last six months. Smithies and Ochsner<sup>4</sup> quote the Fenwicks as stating that approximately one-third of gastric cancer patients have elevations in temperature during some portion of the disease, and give their own figures as 15 per cent of 79 cases.

Besides this data on stomach growths, Musser<sup>5</sup> found that 18 out of 100 cases of cancer of the gall-bladder, and 7 out of 18 cases of biliary tract cancer had fever at some time or other, but felt that in all it was due to the complication of inflammation of the tracts, peritonitis or ulceration. As mentioned above, Freudweiler found that 45 per cent of 38 similar cases had fever.

A review of the subject and one of the very few papers dealing

with it in the last twenty years, is by Pedrini<sup>6</sup> who feels that two types of neoplastic fever should be distinguished—one due entirely to the growth and the other due to some pathological complication. He felt that cancer of the liver and pleura were more apt to be associated with fever than were growths of other organs.

A number of isolated but striking instances of neoplastic fever have been recorded, a few of which will bear mention: James Finlayson<sup>7</sup> in 1888 wrote a clinical note on the "Occurrence of Pyrexia, Shiverings and Pyemia in Cases of Malignant Disease," detailing six out of fourteen instances of malignant disease of the abdominal organs where fever occupied such a prominent place in the symptomatology that in several it was thought to be due to abscess and the tumor mass explored for pus. Marsh<sup>8</sup> found high fever with sarcoma of the kidney in a child, aged nine years, and again in a sarcoma of the femur in a boy of the same age, and adds that "such examples will serve to show that in doubtful cases a high temperature cannot be relied on to prove that a disease is inflammatory rather than malignant." Karsner<sup>9</sup> reported a carcinoma of the rectum in a girl, aged ten years, with fever considered due to a tuberculous peritonitis, and an adenocarcinoma of the liver in a girl, aged eleven years, with fever diagnosed as due to an acute endocarditis.

The significance of fever of varying types accompanying cancer has been noted mostly in the German literature, and they in particular stress the intermittent variety. Wunderlich<sup>10</sup> doubtless was the first, as in 1856 he observed that the fever may be intermittent in character and felt that once it ensued the course of the disease was apt to be very rapid. Libert<sup>11</sup> described a "light and hectic" carcinomatous fever, but to Hampeln<sup>12</sup> of Riga should belong the credit for having pointed out the clinical fact that a high septic intermittent fever with chills and sweats, lasting over long periods and simulating malaria, might be caused by carcinoma. All of his cases were in cancer of the stomach. Although his fever curves were not the typical Pel-Ebstein "Rückfallsfieber," his first observation of 2 cases antedated Pel's paper by one year and Ebstein's by two. Later Anker,<sup>13</sup> Bührig<sup>14</sup> and Kobler<sup>15</sup> reported other instances of this.

Freudweiler in his study divides his material into four classes according to the type of fever. The smallest number, 6 per cent of the febrile, or 1.5 per cent of the whole 475, had a continuous fever, with a diurnal variation of not more than one degree Centigrade. The next infrequent were the malaria-like paroxysms often accompanied by chills and recurring with fair regularity. Fourteen and a half of the febrile or 3.6 per cent of the whole, were of this type. Much more common were occasional rises lasting no longer than three days, and comprising 38.5 per cent of the febrile or 9.3 per cent of all. Most common of all was a remittent or intermittent fever.

This was the predominant type and was present in 41 per cent of the fever cases and 10.1 per cent of all the cancers. His findings are based on 117 instances where he felt conclusively that the fever was due to the cancer alone. Seventy-two others of the 475 showed fever but were not used, since in these other causes were present sufficient to give fever.

There has been considerable speculation as to the cause of the fever and its lack of consistency. Undoubtedly there is a rare but true neoplastic fever but more commonly it seems due to the necrosis and ulceration in the growth. Some hold that it is more frequent in those cases showing extensive ulceration and widespread metastases, although Osler and McCrae felt from the autopsies in their stomach series that these factors made little difference. Freudweiler states that in 64 autopsies on febrile cases, 50 were ulcerated and 14 not.

TABLE I.—DISTRIBUTION OF CASES AND PERIODS OF OBSERVATION.

Organ.	Cases.	Total days in hospital.	Average number of days in hospital.
Stomach . . . . .	74	2330	31.5
Esophagus . . . . .	16	644	40.2
Colon and rectum . . . . .	19	992	52.1
Liver, etc. . . . .	23	850	36.9
Lung and pleura . . . . .	5	267	53.4
Breast . . . . .	21	923	44.0
Uterus . . . . .	41	1052	25.6
Head and neck . . . . .	32	1338	41.8
Prostate . . . . .	7	240	34.2
Total . . . . .	238	8636	36.0

The patients comprising the present study were seen on the University of California service of the San Francisco Hospital between July, 1917, and July, 1922. No questionable cases are included and the majority have been proven by autopsy or tissue examination at operation, although in a minority the diagnosis has been made on clinical evidence alone. Two hundred and thirty-eight cases form the basis of the report, with what might be termed "medical" or internal malignancy making up the greater number. The proportion of cases in the organs involved is shown in Table I. In this and the following tables the viscera are grouped together in nine classes according to the site of origin of the growth. The liver group consists of primary carcinomata of the liver, bile ducts, gall-bladder as well as pancreas. The head and neck group includes those cancers arising in nasopharynx, parotid, jaw, tongue and larynx. No cognizance is taken in this arrangement of metastases; if a growth arose in the stomach but metastasized into the liver and lung, it was classified only under stomach and not under the other two. In Table I is shown also the number of hospital days' residence with the averages for each group. The extremes ran from one to two

hundred and thirty-five days, but only five were in less than forty-eight hours.

In going over the records the point under scrutiny was the question of fever. Temperatures were taken in Fahrenheit, at least twice a day and frequently oftener. Anything over 99° by mouth or 100° by rectum was considered a fever, the rise for the first forty-eight hours after operation and the agonal rise the twenty-four hours preceding death being excluded in the calculations. In 127 cases fever occurred at some time during the hospital stay, but in 36 of these it was definitely due to some obvious cause and not the growth itself. The most common of these were postoperative complications, reactions following radium treatment, pneumonias and other intercurrent infections. The occurrence of these complicating fevers was highest in the esophageal carcinomata and was due to lung and pleural infections from ulceration into the respiratory tract. In 91 instances, or 38.2 per cent of the entire number, fever occurred from no cause other than the neoplasm itself, as far as could be determined, and it is these cases that are under analysis and discussion. One hundred and eleven or 46.4 per cent showed no fever at any time.

TABLE II.—OCCURRENCE OF FEVER.

Organ.	Number of cases.	Afebrile:		Fever not due to complications:		Fever due to obvious complications:	
		No.	Per cent.	No.	Per cent.	No.	Per cent.
Stomach . . .	74	42	56.8	25	33.8	7	9.4
Esophagus . . .	16	7	43.7	4	25.0	5	31.3
Colon and rectum . . .	19	10	52.6	7	36.9	2	10.5
Liver, etc. . . .	23	9	39.1	12	52.1	2	8.8
Lung and pleura . . .	5	2	40.0	3	60.0	0	0
Breast . . . .	21	9	42.9	7	33.3	5	23.8
Uterus . . . .	41	18	43.9	15	36.6	8	19.5
Head and neck . . .	32	10	31.2	16	50.0	6	18.8
Prostate . . . .	7	4	57.1	2	28.6	1	14.3
Total . . . .	238	111	46.7	91	38.2	36	15.1

In Table II are shown the figures for the several groups. It will be noticed that carcinoma of the lung and pleura and of the liver and bile passages carries with it the highest percentage of fever, a fact in agreement with Freudweiler and Pedrini. Cancer occurring in the parts about the neck and throat has likewise a high incidence of fever, possibly due to the large percentage of metastases in this group. The occurrence of fever in the other groups, comprising three-fourths of the entire number, falls in a fairly close range between 25 per cent and 36 per cent, averaging roughly 33 per cent and coinciding fairly well with the figure of Freudweiler's. One observation, frequently made, was the tendency of the temperature to become subnormal the last week or so of life, notwithstanding complications that ordinarily would give rise to fever. On several occasions a purulent peritonitis was found post mortem, that gave no

sign of its existence in the way of increase in temperature or pulse rate.

In considering the type of fever some difficulty was encountered in making a practical classification. Finally three arbitrary divisions were made: isolated rises not lasting more than twenty-four hours, remittent febrile attacks lasting from two days to two weeks with normal periods between, and a prolonged, either continuous or septic fever, persisting for weeks and dominating the clinical picture as a major symptom. The figures are shown in Table III. Iso-

TABLE III.—TYPES OF FEVER.

Organ.	Febrile cases. Number.	Isolated rises. Per cent.	Intermittent fever. Per cent.	Continuous or septic fever. Per cent.
Stomach . . .	25	52.0	36.0	12.0
Esophagus . . .	4	25.0	75.0	0
Colon and rectum	7	85.7	0	14.3
Liver, etc. . .	12	50.0	41.6	8.3
Lung and pleura .	3	66.7	0	33.3
Breast . . .	7	100.0	0	0
Uterus . . .	15	73.3	20.0	6.7
Head and neck .	16	75.0	25.0	0
Prostate . . .	2	100.0	0	0
Total . . .	91	65.9	26.4	7.7

lated rises are by far the most frequent and amount to 60 out of 91, or 65.9 per cent of all febrile cases. The remittent variety comes next with 24 out of 91, or 26.4 per cent, while prolonged fevers are the rarest of all, amounting to 7.7 per cent. This last type is the most interesting and was encountered only 7 times—in 3 stomach cancers, and 1 each of rectum, liver, lung and uterus. Three of these have been reported in detail in a previous note.<sup>16</sup> These results may be expressed another way by saying that 25.2 per cent of all cases showed isolated rises in temperature, 10.1 per cent remittent, and 2.9 per cent continuous pyrexia.

TABLE IV.—FEVER IN METASTATIC CASES.

Organ.	All cases. Number.	Febrile cases. Per cent.	Metastatic cases. Number.	Metastatic cases, febrile. Per cent.
Stomach . . .	74	33.8	44	34.0
Esophagus . . .	16	25.0	6	33.3
Colon and rectum	19	36.9	8	62.5
Liver, etc. . .	23	52.1	13	53.8
Lung and pleura .	5	60.0	3	66.6
Breast . . .	21	33.3	19	31.6
Uterus . . .	41	36.6	34	44.1
Head and neck .	16	50.0	28	50.0
Prostate . . .	7	28.6	2	50.0
Total . . .	238	38.2	157	42.6

As noted above the relationship between metastases and fever often has been mentioned, and the cases were examined carefully as to this point. Again difficulty arose from the fact that but a limited number were available since the absence of metastases could be told only after a complete autopsy. Their presence however usually was readily determined, especially by operation, and those known to have had metastasizing growths are collected in Table IV. The incidence of fever in this group is compared with the incidence of fever in the entire lot and remarkable little discrepancy is found between the two. The only marked difference is in the colon-rectum group where the metastatic cases show a considerably higher proportion of fever than do the others. The prostatic growths were too few to be of any importance in the calculation. The non-metastatic group is very small and therefore hardly available for comparison, but is shown in Table V. With the exception of the single febrile carcinoma of the larynx, and the liver group, there is a slight reduction of the febrile percentages in the others.

TABLE V.—FEVER IN NON-METASTATIC CASES.

Organ.	All cases. Number.	Febrile cases. Per cent.	Non-metastatic cases. Number.	Non-metastatic cases, febrile. Per cent.
Stomach . . .	74	33.8	11	18.1
Colon and rectum	19	36.9	5	20.0
Liver, etc. . .	23	52.1	5	60.0
Lung and pleura	5	60.0	2	50.0
Head and neck	16	50.0	1	100.0
Total . . .	238	38.2	23	33.3

The only statement permissible from these two sets of figures is that the presence of metastases does not seem to alter the occurrence of fever to any extent. This is in agreement with the conclusions of Osler and McCrae, who, from the autopsy cases of stomach carcinoma, felt that the presence of metastases had but little influence on temperature. It may be of interest to note here two remarkably contrasting cases of lung carcinoma. In one, with widespread metastases to lymph nodes, brain, adrenals and opposite lung, there was no fever during the thirty-five day hospital stay, while in the other, reported elsewhere, a carcinoma of the bronchus without metastases, gave rise to the most marked pyrexia of the entire series, the temperature not remaining normal for longer than forty-eight hours in the whole five months' observation.

The question of ulceration likewise is of interest on account of its bearing on fever. Numerous authors state that it predisposes to this, although here again Osler and McCrae found that it had no constant influence on stomach cancer. In the visceral cases the presence or absence of ulceration only could be determined by autopsy, but in the external growths of breast, uterus and neck it



was ascertained by inspection. One hundred and twenty-seven cases are available in this group and the total figures are given in Table VI in comparison with the figures for all cases. Again there is a remarkable agreement between the figures for all growths and the figures for the non-ulcerating growths. The main difference arises from the fact that ulcerations in a neoplasm are very apt to cause infection of adjacent parts with resulting fever, so that we see a considerable increase in the percentage of fevers arising from complications, with a corresponding decrease in the percentage of febrile ulcerating growths as compared to others. The presence of the ulceration in the growth itself increased the incidence of fever from 38 per cent to 45 per cent.

TABLE VI.—FEVER IN NON-ULCERATED AND ULCERATED CASES.

	Number.	Afebrile. Per cent.	Fever not due to complications. Per cent.	Fever due to obvious compli- cations. Per cent.
All cases . . .	238	46.7	38.2	15.1
Non-ulcerated . .	76	47.4	36.8	15.7
Ulcerated . . .	51	29.4	45.1	25.5

**Summary.**—The presence of fever of various types in malignant growths has long been known and more frequently was commented upon in the literature of a generation ago than at the present time.

A series of 238 cases of undoubted carcinomata of various organs was studied to determine the incidence of fever in malignant growths.

Thirty-eight and two-tenths of these showed fever, not due to any known complication, during some time of their hospital stay. The neoplasms of lung and liver gave the highest percentage of fever, while in the other organs fever incidence fell rather closely around 33 per cent. Fifteen and one-tenth per cent showed fever due to some obvious complication, the occurrence of these complications being greatest in cancer of the esophagus.

Isolated rises in temperature were by far the most frequent febrile phenomenon, comprising 65.9 per cent of all febrile cases and 25 per cent of all. Twenty-six and four-tenths per cent of fevers, or 10.1 per cent of the whole, were of the remittent type, and 7.7 per cent of fevers were of the long duration variety. In only 2.9 per cent of all cases did the hyperpyrexia approach a symptom of importance.

The occurrence of metastases did not appear to influence the incidence of fever.

The occurrence of ulceration did not increase the liability to fever except as it produced complicating infections in surrounding structures.

**Conclusion.**—In more than a third of the cases of carcinoma fever may be expected during some period of the illness, but its occurrence as a pronounced feature of the disease is an unusual finding.

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## SCARLET FEVER AS A REACTION OF HYPERSENSITIVENESS TO STREPTOCOCCUS PROTEIN.\*

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### OUTLINE.

- I. INTRODUCTION.
- II. A COMPARATIVE STUDY OF THE CLINICAL FEATURES OF DRUG ALLERGY, SERUM ALLERGY AND SCARLET FEVER.
- III. A STUDY OF THE RELATION OF STREPTOCOCCUS TO SCARLET FEVER.
- IV. EXPERIMENTAL INVESTIGATION.
  - (a) METHODS.
  - (b) MATERIAL.
  - (c) TECHNIC.
  - (d) RESULTS.
- V. DISCUSSION.
  - (a) EPIDEMIOLOGICAL OBSERVATIONS.
  - (b) PRACTICAL APPLICATIONS.
- VI. SUMMARY.

I. Introduction. One of the outstanding, unsolved problems in preventive medicine is that which has to do with the exanthematous diseases of childhood and early adult life. Nothing has been proven as to the exact causes of these diseases and, with the excep-

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tion of vaccination against smallpox, we have as yet to develop adequate methods for their control.

From 1907 to 1917, while in the teaching of bacteriology and hygiene and the practice of clinical medicine, the study of several cases of food, drug and serum "idiosyncrasies," or "anaphylaxis," now better described as "hypersensitiveness," emphasized to the writer the similarity of the clinical signs and symptoms of these conditions to some of the common acute exanthematous diseases. From 1917 to 1921, as State Commissioner of Health in Maine, the further opportunity was presented to study several small outbreaks of scarlet fever, measles and smallpox; and again the impression was gained that one or all of the acute exanthemata might be special manifestations of specific protein hypersensitiveness. Because of the highly communicable nature of these diseases, it was at once conceived that the only logical theory to explain their etiology from the standpoint of hypersensitiveness must be one that assumes the proteins involved in sensitization and intoxication to be derived from the autolysis of various known or unknown microorganisms. A brief preliminary statement of this hypothesis was published by the writer<sup>1</sup> in 1917. A few suggestions of a similar nature have been noted in a recent study of the literature.<sup>50</sup>

**II. A Comparative Study of the Clinical Features of Drug Allergy, Serum Allergy and Scarlet Fever.** Before proceeding to a consideration of certain experiments to test such a theory, particularly as it regards scarlet fever, it will be of interest to compare the clinical characteristics of drug allergy and serum allergy (forms of allergic hypersensitiveness) with those of scarlet fever, in all three of which a suggestive parallelism is evident. At this time it is impossible to go into all of the details concerning the subject of hypersensitiveness to bacterial and other proteins or the subphenomena of anaphylaxis and allergy, a review of which may be obtained from such recent excellent summaries as that of Coca.<sup>2</sup> In passing, we would particularly emphasize again that hypersensitiveness may be caused by bacterial proteins as well as by proteins from other sources.

A study of Table I shows that these three conditions, drug allergy, serum allergy and scarlet fever, have strikingly similar clinical signs and symptoms which may appear singly or in combination. Each condition is characterized by an incubation period of variable length; a chill with headache and general malaise marks the onset in many cases; dyspnea is frequent in occurrence; more or less fever and vomiting are evident; skin eruptions, followed by more or less desquamation, are characteristic; fall in blood-pressure has been noted; eosinophilia is common to all three; local or general edema, lymph gland and joint involvement and albuminuria are frequently present; shock, loss of consciousness or a fatal termina-

TABLE I.—COMPARISON OF CHARACTERISTIC SIGNS AND SYMPTOMS OF DRUG ALLERGY, SERUM ALLERGY AND SCARLET FEVER.

Characteristic signs and symptoms.	Drug allergy.	Serum allergy.	Scarlet fever.
Incubation period	Variable, two hours to twenty days. Generally short	Variable, few hours to twenty-four days. Average ten to twelve days	Variable, two to four days. Some instances of ten to fourteen days average.
Chill	Frequent	Frequent	Frequent.
General malaise and headache	Frequent	Frequent	Frequent.
Dyspnea	Frequent	Frequent	Frequent.
Fever	Frequent; may reach 106° or more	Frequent; 106° or more	Common; usually high.
Vomiting	Frequent	Frequent	Frequent.
Angina	Absent; difference in "portal of entry" and primary lesion	Absent; difference in "portal of entry" and primary lesion	Common; throat and tonsils probable initial or primary lesion.
Skin eruption	Common; varies in character. Frequently "scarlatiniform." General over body. May first be local following hypodermic injection.	Common; first local around site of injection. Later generalized. Frequently "scarlatiniform."	Common; first local over front and sides of neck and on upper chest. Adjacent to portal of entry (throat or tonsils). Becomes general.
Skin desquamation	Fairly common, fine scales to large flakes or even casts of hands, etc.	Typical in some cases	Common.
Edema	Fairly common; local (face) or general	Fairly common; local (face) or general	Fairly common; local (throat or face) or general.
Eosinophilia	10 to 15 per cent increase in most cases	Cases reported, 10 to 14 per cent increase in experimental food allergy	As much as 20 per cent increase.
Lymph gland involvement	Frequent	Frequent	Frequent.
Joint involvement	Frequent	Frequent	Frequent.
Albuminuria	Frequent	Frequent	Frequent.
Fall of blood-pressure	Few cases reported	Cases reported	Frequent.
Shock and fatality	Occasional	Occasional	Frequent, in "malignant" type.
Protection	In some cases a "tolerance" is established	Common after recovery from "shock." Not always permanent	Common after recovery. Not always permanent.
Inheritance of susceptibility	Positive evidence in some cases	Positive evidence in some cases	Positive evidence in some cases.
Therapy	Condition improves on discontinuance of drug	Adrenalin and atropine of value	Adrenalin of value in severe cases. Atropine may lessen susceptibility.

tion at times occur; following recovery, or an establishment of tolerance, more or less protection at least temporarily is induced; in several instances hereditary susceptibility has been noted; therapeutic benefit has been derived from the same drugs. Regarding the signs and symptoms of hypersensitiveness in general, Coca<sup>3</sup> states that "They are uniform in any one species for various substances." On this basis the almost complete uniformity in the signs and symptoms of these three conditions in man is definitely suggestive that not only are drug allergy and serum allergy specific forms of hypersensitiveness but that scarlet fever also may be a manifestation of a specific hypersensitiveness. It must be admitted that a few authorities do not agree that so-called drug idiosyncrasies are based on conditions of hypersensitiveness. However, the hypothesis advanced by several of the most noteworthy investigators—that drug reactions may be based on an abnormal alteration of blood and tissue proteins by the chemical, thus *acting* as foreign protein to the injected animal or affected person—has much to commend it.

It would be without profit at this time to make a detailed study of all the above-mentioned signs and symptoms as they relate to each disease. It may, however, be said that no one sign or symptom is pathognomonic of any one of the three conditions. The signs and symptoms, as a whole, must be taken into consideration in reaching a diagnosis, and even then it is often very difficult to be positive as to the nature of the disease in question. Frequently the history must be relied upon to determine the possible taking of a drug, the injection of a serum or an exposure to scarlet fever or a septic infection. The one feature of the three conditions which seems, and which might logically be expected, to vary considerably in each is that of the portal of entry, or local primary reaction; in scarlet fever this apparently is in the mouth, throat or tonsils, giving rise to the typical angina and "strawberry" tongue, accompanied by the exanthem which first shows itself on the neck and upper chest, that is, in the immediate vicinity of the portal of entry. In so-called "traumatic scarlet fever" due to injuries, burns, etc., or "postoperative scarlet fever" the exanthem, as a rule, starts adjacent to the wound, burn or operation site; in "puerperal scarlet fever" the eruption first appears in the neighborhood of the generative organs, that is, on the lower abdomen and upper part of the thighs. If a drug or a serum is injected, and is followed by evidence of hypersensitiveness, the eruption usually appears first around or near the injection site. It is evident, therefore, that the history of the case, a knowledge of the local "portal of entry" and of the exact site of the primary lesion or reaction, and of the first local manifestation of the eruption are of chief importance in the differential diagnosis of these three conditions.

The most spectacular signs that may be present in drug allergy, serum allergy and scarlet fever, and which it might be well to consider a little more in detail, are found in the skin in the form of eruption and desquamation and in the blood in the form of eosinophilia. Drug and serum allergy may be accompanied by erythematous, urticarial, vesicular, macular, papular, hemorrhagic, morbilliform or scarlatiniform rashes, the latter two being particularly evident following certain drugs and also in serum allergy. Desquamation, or exfoliation of the skin, following a rash may be present in all three of these conditions. It is a mistake to insist that desquamation alone is a pathognomonic sign of scarlet fever. Serum allergy, especially severe cases, may be followed by a certain amount of scaling of the skin, and very definite desquamation has been noted following the eruptions caused by such drugs as antipyrin, chloral hydrate, chloralamide, quinine, salicylic acid, copaiba, digitalis, mercury and morphia.

Pye-Smith<sup>4</sup> reports a case of a man who had taken 40-grain doses of chloralamide every night for twelve nights. On the thirteenth day a diffuse bright red scarlatiniform eruption appeared on the face and soon became general, including the mucous membranes. The temperature reached 103° F. The eruption lasted a week and was followed by a large, flaky desquamation. Stelwagon<sup>5</sup> reports a case of drug allergy following the taking of  $\frac{1}{6}$  grain of quinine by mouth. A general scarlatiniform rash appeared and was followed by characteristic desquamation. In another case<sup>6</sup> of quinine allergy casts of the hands and feet were thrown off and exfoliation persisted for weeks. It has been shown<sup>6</sup> that desquamation also may follow copaiba eruptions, but only when the drug is continuously administered. In other words, the element of time as well as severity must be considered in explaining the causation of desquamation following various eruptions. In a case<sup>6</sup> of digitalis allergy an eruption was followed by desquamation in large flakes and complete shedding of hair and nails.

In drug allergy an eosinophilia to the extent of 10 to 15 per cent increase has been noted.<sup>7</sup> A definite eosinophilia has been found<sup>8</sup> also in experimentally produced food allergy in guinea-pigs. It has been demonstrated by others<sup>9</sup> to be present in cases of serum allergy. Berger<sup>10</sup> reports an eosinophilia occurring in breast-fed infants following the ingestion of a foreign protein, such as cows' milk. Herrick<sup>11</sup> was able to develop a notable eosinophilia in guinea-pigs by the intraperitoneal injection of an aqueous extract of *ascaris lumbricoides* and he believes the substance causing such an increase of eosinophils to be a protein. A marked increase in the number of eosinophils has been found associated with hay-fever, eczema, urticaria and asthma, due to protein sensitization, and with animal parasitic infestation. Clarke and Meyer<sup>12</sup> report an interesting case of hypersensitiveness

to silk in which the blood revealed 10.5 per cent eosinophils. Although we have no detailed information as to how it is brought about, the general opinion of the best authorities is that all of these instances of eosinophilia are associated with some form of specific hypersensitiveness. In fact, Schlecht<sup>13</sup> concludes that eosinophils have the special function to protect the body against the invasion of a foreign protein. The work of others, also, indicates that an increase in the percentage of eosinophil cells in the blood is evidence of sensitization to a protein, either by subcutaneous, intravenous or natural routes, such as through the mucous membrane. An important factor in such eosinophilia is that of the time element. As a rule, such increase of eosinophils takes place only after a variable period of time following the introduction of an alien protein or sensitizing agent, and though frequently persistent it may be only of short duration. It is usually a feature of the so-called posthypersensitive stage.

As Moschcowitz<sup>14</sup> states: "The relation of eosinophilia to anaphylaxis suggests, perhaps, that other diseases commonly associated with eosinophilia may be regarded as anaphylactic in nature." With this demonstrated relation of eosinophilia to hypersensitiveness in mind, it is at least very suggestive to find that an eosinophilia is rather characteristic of the later stages of scarlet fever. While the average percentage of eosinophils in the blood of a perfectly normal person may be from 2 to 4 per cent, Emerson<sup>15</sup> states in regard to the eosinophils that: "In scarlet fever these cells may vary from 8 to 15 per cent." Holt,<sup>16</sup> in describing the blood in scarlet fever, tells us that "During the first week the eosinophils are diminished; after the fifth or sixth day there is rapid increase in the eosinophils which attain their maximum, sometimes 20 per cent of the total leukocytes, between the fourteenth and twenty-first days. After the third week they gradually diminish."

**III. A Study of the Relation of Streptococcus to Scarlet Fever.** Without attempting to cite all of the literature and evidence for or against the etiological relation of the streptococcus, either as a special group or in general, to scarlet fever, the following statement of Bergé,<sup>17</sup> made in 1895, must be given serious consideration: "An imposing array of evidence points to the streptococcus in one of its virulent forms as the pathogenic agent of the disease." More recently Bliss<sup>18</sup> states that he has found hemolytic streptococci in 100 per cent of the throats of patients with scarlet fever during the first week of the disease, and that these organisms are present in the throat for an average period of from ten to twenty days. While no morphological or cultural characteristics have been demonstrated that seem to differentiate the hemolytic streptococcus associated with scarlet fever from other types of *Streptococcus pyogenes*, Bliss believes that from the standpoint of serological

reactions hemolytic streptococci found in scarlet fever throats may constitute a single biological group. Be this as it may, up to the present time the attitude of the "court" of scientific investigation has been that the streptococcus is "innocent" of being the cause of scarlet fever until "proven guilty," and convincing, final proof has not been forthcoming. Strong circumstantial evidence is at hand but it has not been considered sufficient. Many, if not most, of the authorities assume that some mysterious "advance agent" goes with or ahead of the streptococcus and prepares the way for the latter; in other words, that this agent—the supposed primary etiological factor—and the streptococcus are in symbiosis or "partnership." Why complicate the problem in this way until we have exhausted all the possibilities of the streptococcus, or its autolytic products alone, as the primary etiological factor in scarlet fever?

The chief arguments against the idea that streptococcus is the cause of scarlet fever may be enumerated as follows:

1. The inoculation of streptococcus into healthy individuals apparently has not caused the typical disease, scarlet fever.

2. Streptococcus infection does not, as a rule, confer an immunity to subsequent infection, while in most instances an attack of scarlet fever apparently does protect against subsequent attacks.

3. In cases of uncomplicated scarlet fever, in which death has occurred on the second or third day the blood and internal organs usually are found to be sterile.

In answer to the first argument, from the standpoint of our hypothesis, it may be said that in the comparatively few experiments in an attempt to cause scarlet fever in healthy individuals by inoculation with streptococcus, such persons may not have been hypersensitive to streptococcus protein and hence naturally would not show any evidence of an anaphylactic or allergic attack.

On the other hand, the injection of "prophylactic" streptococcus vaccine, made up of dead organisms, according to Gabritschewsky,<sup>19</sup> in from 10 to 15 per cent of his cases *has* resulted in a scarlatini-form eruption at the site of injection often followed by a general eruption, associated with fever and many of the other symptoms of typical scarlet fever. Kogan<sup>20</sup> obtained similar results in 9 out of 62 children following the administration of streptococcus vaccine. Krumweide's<sup>21</sup> assistant accidentally swallowed a suspension of streptococci. Two days later this assistant developed a sore throat followed by all the so-called classic symptoms of scarlet fever, including desquamation. There had been no known contact with a case of scarlet fever. Unless all of these instances were simply coincidental cases of scarlet fever (an unwarranted assumption) it must be admitted that scarlet fever, at least of a mild nature, *may be and has been* thus artificially produced in certain persons hypersensitive to streptococcus protein.



Regarding the second argument that streptococcus infection does not confer an immunity while scarlet fever usually does, it may be said that although the *infection* with streptococcus may not result in protection, *protein sensitization and intoxication* from the autolysis of this organism theoretically *should* result in more or less antianaphylactic protection, as is the case following recovery from acute attacks of anaphylactic or allergic shock or following experimentally produced bacterial hypersensitiveness.

This refractory state, or antianaphylaxis, is not necessarily permanent nor absolute. However, animals experimentally injected do not show the same degree of hypersensitiveness thereafter, symptoms if present being mild and rarely leading to a fatal result. Moreover, it is quite possible that in scarlet fever the protection following one attack may be more *apparent* than real. In other words, the power to react may have been changed to such an extent that subsequent attacks have such a short incubation period, and are so mild and "fleeting" in character, that their real nature is not evident. Such an accelerated or immediate reaction may be protective, and may depend on the original hypersensitiveness, just as a primary reaction or "take" follows the first successful vaccination against smallpox, while in a subsequent vaccination the incubation period may be much shortened and the clinical features lessened or apparently absent. On the other hand, relapses and second attacks of scarlet fever are not so very uncommon, indicating in such instances a possible continuance or return of a mild hypersensitiveness in this disease.

The fact that the blood or internal organs in cases of scarlet fever frequently are found to be sterile before or after death, even on the second or third day of the disease, may not necessarily weaken our theory. In fact this is what might be expected if scarlet fever is merely a manifestation of a streptococcus protein hypersensitiveness. Streptococci may remain localized in the throat or tonsils as the "primary lesion" or "portal of entry" in typical, uncomplicated scarlet fever, as suggested by Bergé;<sup>17</sup> or they may remain localized in the uterus (in puerperal scarlet fever), wounds (traumatic scarlet fever), operation sites (surgical scarlet fever), burns (scarlet fever following severe burns). Rose-nau and Anderson<sup>22</sup> state that "When bacteria grow in the body they are dissolved by lytic agencies, and the foreign protein in the individual germ cells may sensitize the body and afterward poison it." From these local sites, or primary lesions, such as the throat or uterus, following the autolysis of streptococci, protein molecules may be absorbed in sufficient amount to give rise to typical signs and symptoms of scarlet fever in hypersensitive individuals. In other words, these local areas, portals of entry, or primary lesions, may be analogous to the local sites of experimental injection of various substances in the artificial production of anaphylaxis or

allergy. That these "extrafaucial" cases of scarlet fever are identical in general nature and etiology with typical cases of the disease was formerly much doubted. However, many of the leading authorities have become convinced that the scarlatinoid eruptions following cutaneous burns, operations and the puerperium represent in reality the exanthem of scarlet fever. In fact, Schamberg<sup>46</sup> cites an interesting case in which a nurse contracted a typical case of scarlet fever from a boy whom she was nursing, this boy having developed the disease in connection with a severe burn on the face and arm. The child showed no characteristic signs in the throat or on the tongue.

Based on the above brief comparative study of the clinical signs and symptoms of drug allergy, serum allergy and scarlet fever and of the relation of streptococcus to scarlet fever, an account will now be given of certain experimental investigations.

**IV. Experimental Investigation.** A. METHODS. In this experimental investigation it was decided to make use of the ordinary cutaneous test to determine whether or not scarlet fever gives evidence of being a reaction of specific protein hypersensitiveness. Having in mind the very definite relation of the streptococcus to scarlet fever, as outlined previously, it seemed logical to test the sensitiveness of scarlet fever patients and normal controls to streptococcus protein.

In this procedure several factors must be kept in mind: (1) As suggested by Schloss,<sup>8</sup> in testing for allergy a negative cutaneous test is not always conclusive, and for various reasons. Such a negative test may be due to a lack of *skin* sensitization in certain individuals or to an occurrence of a temporary general desensitization of the body during or after an attack or treatment of protein sensitization. For example, Schloss demonstrated in infants showing an original positive cutaneous sensitization to egg and milk, that after marked signs and symptoms, including urticaria, had occurred (following ingestion of these proteins) the cutaneous reaction immediately disappeared for variable periods of time. In other words, the original cutaneous sensitiveness was destroyed by the general reaction. Our experiments and deductions herein noted are based primarily on these findings of Schloss. (2) Such cutaneous tests may vary considerably in intensity or grades of reaction and in the time interval after the test has been made. Thus, Longcope<sup>23</sup> found that in cases of urticaria or eczema due to protein sensitization the interval between the test and the skin reaction may be prolonged. He showed also that in such cases the skin reactions are not always obtained, in fact may be rare unless the intracutaneous method is used. Others have demonstrated, however, that the intracutaneous test may be non-specific in some cases. In fact, Walker<sup>25</sup> believes that the intradermal test is too delicate, if not actually non-specific, and he suggests

that the linear scratch cutaneous test probably is more reliable. In this work, therefore, it was decided to use only the linear and rotating scratch cutaneous tests. Based on the experiments of Schloss, it was considered necessary to keep in mind the fact that if scarlet fever is a reaction to a streptococcus protein hypersensitiveness, such tests on patients in various stages of scarlet fever might or probably would result in negative or, at most, weakly positive reactions, because of desensitization or antianaphylaxis, at least temporarily induced. It would then become necessary to determine if possible any later reappearance of hypersensitiveness and any change in degree or intensity of the same. Moreover, it would be of interest to note the relative sensitiveness to streptococcus protein of persons who have had scarlet fever at some time in the past compared with normal controls giving no history of the disease.

**B. MATERIALS.** Cases of scarlet fever, as well as individuals, giving both positive and negative past histories of the disease for controls, were put at my disposal by the Minneapolis General Hospital and the University of Minnesota Health Service, due acknowledgment of which is made later.

Bacterial proteins for the tests were obtained from H. K. Mulford Company in the form of so-called "Bacteria Dried." These are described by the Mulford Laboratories as "Proteins prepared from mass cultures of specific bacteria, killed, mixed, dried and ground to a fine powder. 'Bacteria Dried' are used in cutaneous tests to determine the sensitiveness of individuals to any one of the groups of bacteria, which, in many instances, have been found to be the cause of asthmatic symptoms and complications of pollen hay-fever."

As to the source of the streptococci used in the preparation of the so-called "Streptococcus Dried" it is stated<sup>24</sup> that they are "Mostly from hemolytic strains collected from various sources and contain streptococci isolated from scarlet fever throats." As to the method of killing these organisms, it is stated that "They are submerged in a tank of water in sealed bottles containing about 500 cc. These bottles are firmly held in an apparatus which revolves beneath the water, and the agitation insures that all organisms in the bottle are evenly heated. The temperature of the tank is 60° C. for one hour."

**C. TECHNIC.** 1. As a first group, experiments were tried on 35 patients in various stages of scarlet fever. Most of these patients were tested by a slight modification of the linear scratch cutaneous method recommended by Walker,<sup>25</sup> while a certain proportion were tested by the well-known rotating scarification method.

2. A second group of controls, made up of 48 persons not having the active disease, were tested by the linear scratch method. This group was further subdivided into two series: One made up of

31 persons, giving no history of scarlet fever, and the other consisting of 17 individuals who had had the disease at some time in the past. Since this linear scratch method gave a rather high percentage of positive reactions in these controls, it was not thought necessary to check them with other more delicate methods.

For the linear scratch tests, sharp, sterile sewing needles of average and uniform size were used. On the right upper forearm (after the usual cleansing) a superficial scratch  $\frac{1}{4}$  inch long was made to serve as a control without streptococcus protein. On the left upper forearm (after like cleansing) a scratch of the same nature and size was made, and into the exuding lymph along this scratch was gently, but thoroughly, rubbed a quantity of dried streptococcus protein which could be held in the "eye" of the needle.

The rotating scarification or abrasive test consisted of two abrasions on the left forearm of the patient, made with a skin-borer following the cleaning of the skin. One of these denuded areas was left as a control, while into the other an amount of dried streptococcus protein, which could be carried in the "eye" of an average sized sterile needle, was gently but thoroughly rubbed.

In most cases the dried streptococcus protein alone was rubbed into the exuding lymph, covering the scratch or abrasion; in a few cases a drop of  $\frac{N}{10}$  sodium hydrate was added. There seemed to be no difference in the results from this standpoint.

D. RESULTS. The results of these tests were inspected at various hourly and daily intervals up to a week or more. Only positive and negative results are here reported. All cases of questionable or doubtful positive reaction are included as negative.

A positive reaction following the scratch cutaneous test in these experiments is one which consists of definite infiltration and elevation of the scratch and the immediately surrounding tissue, in some cases in the form of an elongated "wheal," together with a secondary areola of redness or erythema of irregular outline. This area of elevation and redness varies in diameter, but only those reactions are designated as positive in which the diameter is  $\frac{1}{2}$  inch or more. In a few instances a very faint and narrow area of redness appeared about the scratch, but such were termed negative. All controls without protein were absolutely negative, while in most instances all tests with protein designated as negative were clearly negative; that is, nothing persisted except the original scratch line, unassociated with infiltration, elevation or a surrounding erythema. It was noted that when the test was made early in the disease, that is, during the first few days while a generalized scarlet fever eruption was present, the result was clearly negative. Questionable or doubtful positive reactions (designated as negative) appeared only in those cases tested during the last days of convalescence.

Positive reactions in the control individuals appeared in from four to eighteen hours, reached a point of maximum intensity in twenty-four to forty-eight hours, and then faded rapidly in three or four days, leaving little or no discoloration or scaling.

By reference to Table II it will be noted that out of 35 cases of scarlet fever, in various stages of the disease, tested with streptococcus protein by cutaneous methods no case developed a clearly positive reaction. All were negative, as were the controls without protein.

TABLE II.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 35 ACTIVE CASES OF SCARLET FEVER.

Case.	Sex.	Age.	Clinical diagnosis.	Duration of illness.	Method of test.	Protein used.	Result.	
							Protein test.	Control test.
V. B.	M.	19	Sc. fever.	3 days	Scratch	Streptococcus	Negative	Negative.
L. A.	M.	18	"	1 "	"	"	"	"
F. C.	M.	17	"	3 "	"	"	"	"
D. L.	M.	7	"	8 "	"	"	"	"
B. N.	M.	8	"	8 "	"	"	"	"
M. F.	M.	4	"	7 "	"	"	"	"
L. A.	M.	7	"	5 "	"	"	"	"
G. S.	F.	29	"	15 "	"	"	"	"
E. W.	M.	33	"	6 "	"	"	"	"
I. H.	F.	26	"	24 "	"	"	"	"
D. E.	F.	30	"	25 "	Abrasive	"	"	"
A. L.	F.	26	"	29 "	"	"	"	"
M. B.	F.	18	"	16 "	"	"	"	"
H. P.	F.	18	"	6 "	"	"	"	"
F. F.	F.	13	"	19 "	"	"	"	"
L. A.	M.	7	"	13 "	"	"	"	"
M. F.	M.	4	"	15 "	"	"	"	"
B. N.	M.	8	"	16 "	"	"	"	"
D. B.	M.	7	"	16 "	"	"	"	"
S. R.	M.	9	"	16 "	Scratch	"	"	"
S. L.	F.	3	"	5 "	"	"	"	"
A. A.	M.	3	"	17 "	"	"	"	"
T. T.	M.	9	"	4 "	"	"	"	"
M. J.	F.	24	"	15 "	"	"	"	"
J. C.	M.	23	"	5 "	"	"	"	"
P. D.	F.	20	"	3 "	"	"	"	"
M. B.	F.	8	"	21 "	"	"	"	"
M. W.	F.	17	"	16 "	"	"	"	"
L. R.	M.	2	"	9 "	"	"	"	"
V. A.	M.	5	"	6 "	"	"	"	"
G. B.	M.	21	"	2 "	"	"	"	"
M. P.	F.	8	"	9 "	"	"	"	"
R. T.	F.	25	"	9 "	"	"	"	"
P. N.	M.	27	"	9 "	"	"	"	"
A. P.	F.	32	"	11 "	"	"	"	"

A study of Table III brings out the fact that of 17 persons giving a positive history of having had scarlet fever at some time

in the past, 7, or 41 per cent, showed a positive reaction, while 10 gave a negative reaction when tested with streptococcus protein by the scratch cutaneous method, all control tests without protein being negative.

TABLE III.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 17 INDIVIDUALS GIVING PAST HISTORY OF SCARLET FEVER.

Case.	Sex.	Age.	History scarlet fever.	Years since disease.	Method of test.	Protein used.	Results.	
							Protein test.	Control test.
A. O.	M.	23	Positive	1*	Scratch	Streptococcus	Negative	Negative.
V. S.	M.	17	"	1*	"	"	Positive	"
C. L.	M.	18	"	1*	"	"	Negative	"
M. W.	M.	20	"	1*	"	"	Positive	"
P. H.	M.	24	"	1*	"	"	Negative	"
A. R.	M.	17	"	1*	"	"	"	"
I. K.	M.	18	"	1*	"	"	Positive	"
C. K.	M.	18	"	1*	"	"	"	"
M. S.	M.	19	"	1*	"	"	Negative	"
P. B.	M.	17	"	1*	"	"	"	"
C. N.	M.	16	"	Several	"	"	Positive	"
M. S.	F.	25	"	"	"	"	Negative	"
M. G.	F.	27	"	"	"	"	Positive	"
A. V.	M.	21	"	"	"	"	Negative	"
F. D.	M.	22	"	"	"	"	Positive	"
B. H.	M.	22	"	"	"	"	Negative	"
P. R.	M.	18	"	"	"	"	"	"

\* Cases thus marked had scarlet fever one year ago in the same epidemic.

A third group of persons, who gave no history of scarlet fever in the past, were tested and the results noted in Table IV. Out of 31 persons tested with streptococcus protein by the scratch cutaneous method, 19, or 61 per cent, showed a positive reaction and 12 a negative reaction. All controls were negative.

A general summary of these reactions is given in Table V, comparing the negative reactions in 35 active cases of scarlet fever with 41 per cent of positive reactions in 17 individuals who had scarlet fever at some time in the past (several of them within one year) and 61 per cent of positive reactions in 31 persons who never had the disease.

Is it not significant that all active cases of scarlet fever in these experiments showed a negative reaction, while normal controls, those not having the active disease, showed a rather high percentage of positive reactions? Schloss<sup>8</sup> states that "Sufficient evidence has accumulated to make it reasonably certain that a positive skin reaction in the presence of negative control tests is indicative that the patient is sensitive to the protein to which it

reacts." From this standpoint we may state that those apparently normal persons in our experiments who gave a positive reaction were sensitive to streptococcus protein, and it suggests that a certain percentage of all persons (either those who have had scarlet fever in the past or who have not had it) may be sensitive to this particular protein. It is of interest to note further

TABLE IV.—CUTANEOUS SENSITIZATION TESTS WITH STREPTOCOCCUS PROTEIN ON 31 INDIVIDUALS GIVING NO HISTORY OF SCARLET FEVER.

Case.	Sex.	Age.	History of scarlet fever.	Present condition.	Method of test.	Protein used.	Results.	
							Protein test.	Control test.
A. J.	M.	21	Negative	Normal	Scratch	Streptococcus	Negative	Negative.
C. N.	M.	19	"	"	"	"	Positive	"
R. O.	M.	16	"	"	"	"	Negative	"
R. W.	M.	17	"	"	"	"	"	"
R. C.	M.	19	"	"	"	"	Positive	"
M. T.	F.	20	"	"	"	"	"	"
M. O.	F.	21	"	"	"	"	"	"
A. F.	M.	17	"	"	"	"	Negative	"
L. K.	M.	17	"	"	"	"	Positive	"
C. W.	M.	17	"	"	"	"	Negative	"
F. S.	M.	20	"	"	"	"	Positive	"
N. U.	M.	16	"	"	"	"	"	"
L. B.	M.	18	"	"	"	"	"	"
H. J.	M.	17	"	"	"	"	"	"
F. W.	M.	19	"	"	"	"	Negative	"
D. L.	M.	16	"	"	"	"	Positive	"
W. D.	M.	19	"	"	"	"	"	"
L. C.	M.	20	"	"	"	"	Negative	"
D. G.	F.	21	"	"	"	"	"	"
R. P.	M.	20	"	"	"	"	Positive	"
V. T.	M.	19	"	"	"	"	"	"
W. O.	M.	26	"	"	"	"	"	"
R. W.	M.	23	"	"	"	"	"	"
S. F.	M.	18	"	"	"	"	"	"
W. J.	M.	20	"	"	"	"	Negative	"
H. J.	F.	22	"	"	"	"	Positive	"
L. F.	F.	18	"	"	"	"	Negative	"
M. R.	F.	19	"	"	"	"	"	"
M. S.	F.	24	"	"	"	"	Positive	"
D. A.	F.	18	"	"	"	"	Negative	"
R. B.	M.	18	"	"	"	"	Positive	"

TABLE V.—SUMMARY OF ALL CASES TESTED WITH STREPTOCOCCUS PROTEIN (35 CASES OF SCARLET FEVER AND 48 CONTROLS).

Nature of cases.	Number tested.	Number positive.	Number negative.	Per cent positive.
Cases of active scarlet fever . . . . .	35	0	35	0
Individuals giving past history of scarlet fever . . . . .	17	7	10	41
Individuals giving no history of scarlet fever . . . . .	31	19	12	61

that there was a larger percentage of positive reactions in those who had never had scarlet fever than in those who gave a past history of the disease. It may be that in the individuals of the latter group, although originally hypersensitive, the cutaneous reaction of hypersensitiveness disappeared for variable periods of time in the process of desensitization from scarlet fever, to return in some and not in others.

In view of the uniformly negative reactions in the 35 active cases of scarlet fever tested, it is conceivable that in such individuals the cutaneous sensitiveness to streptococcus protein has been destroyed, at least temporarily, by the reaction; such a reaction showing itself in the form of the characteristic signs and symptoms of scarlet fever. If this is so it is additional evidence to warrant the hypothesis that scarlet fever is nothing more than a reaction of hypersensitiveness to streptococcus protein. It must, of course, be kept in mind that such negative reactions may be non-specific in nature.

The question arises naturally, Is this positive reaction to streptococcus, found in our control experiments among fairly normal persons, one of hypersensitiveness, or is it a toxic, inflammatory effect analogous to the true positive Schick reaction in diphtheria? The evidence would seem to indicate that it is a reaction of hypersensitiveness to streptococcus protein. For example, if it were a toxic reaction, due to streptococcus, then, as is the case in a negative Schick test (where it is known that a negative test is evidence of immunity against diphtheria because natural antitoxin in the person's blood has neutralized the injected toxin, thus preventing its inflammatory action), so in a case of active scarlet fever with a negative test to streptococcus protein (as found in all cases of our study), it must be assumed if the test is toxic in nature that such a negative test is an indication of natural immunity or resistance to the toxic action of streptococcus. This argument, however, is not tenable. Considering the very definite etiological relation of streptococci to various complicating lesions of scarlet fever, it hardly can be argued that a person with scarlet fever has a specific immunity or resistance against the toxic products of streptococci.

Other factors which possibly indicate the anaphylactic or hypersensitive nature of the above described cutaneous reactions are their appearance and time of development. The positive Schick reaction (which is not "anaphylactic" in nature, but which is a typical example of a reaction of tissue to a toxic injury) appears as a trace of redness at the site of injection in twelve to twenty-four hours, becomes larger and more distinct in twenty-four to forty-eight hours, and reaches its point of maximum intensity on the third or fourth day, when it shows a rather circumscribed area of redness with some infiltration. It persists from five to



fourteen days and then fades, leaving a brownish, scaling area which may be evident for several weeks

The cutaneous reaction in our experiments, unlike the true Schick reaction, when positive has much the appearance and time of onset of the "pseudo-Schick" reaction (which is considered by most authorities to be a "hypersensitive" reaction). It usually appears early, four to eighteen hours; reaches its height in twenty-four to forty-eight hours; fades rather rapidly in three to four days, leaving little or no discoloration or scaling. At its height it is raised and dark red at the center, graduating off into a more or less secondary areola which is not definitely circumscribed, but has an irregular outline.

While the writer does not wish to imply that these experiments (limited as they are in number) are in themselves conclusive, it would seem that the results (considered in conjunction with the facts previously noted as to (1) the similarity of the signs and symptoms of scarlet fever to those of such manifestly "hypersensitive" states as drug and serum allergy, and (2) the admitted association of streptococci with scarlet fever) lend support to the thesis that scarlet fever is a generalized reaction of hypersensitivity to streptococcus protein.

**V. Discussion.** **A. EPIDEMIOLOGICAL OBSERVATIONS.** From the standpoint of our hypothesis it is obvious that two persons may react differently to virulent human streptococci implanted in the throat or tonsils. One may develop a simple inflammatory reaction to the streptococcus infection resulting in a mild angina or a typical septic sore throat; but with no further marked constitutional signs to indicate hypersensitivity to streptococcus protein (such a person being non-sensitive to this particular protein). The other individual may show not only a mild or severe sore throat as a result of the inflammatory reaction, but (being hypersensitive to the protein molecules of streptococcus, liberated through autolysis) also may show a scarlatiniform rash and other "hypersensitive" signs and symptoms typical of scarlet fever. Thus, scarlet fever might be described as a *compound* condition, made up of a streptococcus infection (either faucial or extrafaucial) plus an intoxication in a person who is hypersensitive to streptococcus protein. Many years ago Jenner<sup>26</sup> asked the question in regard to such diseases as scarlet fever: "May we not conceive than many contagious diseases now prevalent among us may owe their present appearance not to a simple but to a *compound* origin?" On this basis, it is suggested that the beginning, local symptoms of scarlet fever, such as angina, are due to an original streptococcus infection, while all other constitutional signs and symptoms of the disease are due to the autolysis of streptococci and the absorption of streptococcus protein, giving rise to a specific reaction of hypersensitivity in those who are susceptible.

Such an interpretation of scarlet fever would explain not only the demonstrated relation of streptococci to the disease, but also would make clear the many cases of the disease apparently arising *de novo*—those unassociated with or unexposed to other typical cases. Such instances of scarlet fever may be considered to arise in hypersensitive persons who have been infected with streptococci from various virulent streptococcal lesions or from streptococcus "carriers." Scarlet fever following contact with objects associated in time past with cases of the disease may be due to the transfer of streptococci to hypersensitive individuals, giving rise to streptococcal protein intoxication. Scarlet fever appearing in individuals, such as physicians and nurses, who previously have been apparently "immune" to the disease may be explained on the ground that such persons heretofore not "sensitive" have become "sensitized" to streptococcus protein.

The varying severity of scarlet fever, in the light of such a theory, may be due to various grades of hypersensitiveness to, and the "dosage" of, streptococcus protein. It has been demonstrated by various investigators that anaphylactic or hypersensitive conditions depend largely on quantitative factors. In other words, the larger the amount of foreign protein absorbed the greater the reaction in those who are hypersensitive. In this connection it is of interest to note the fact that, as a rule, the severity of scarlet fever apparently varies with the number of streptococci found in the throat. Malignant cases are usually associated with enormous numbers of virulent hemolytic streptococci, while mild cases are associated with comparatively small numbers. It must be kept in mind, also, that such living streptococci constitute a constantly reproducing source of protein poison. The further observation that not all persons intimately exposed to the disease contract it (not over 40 per cent according to some authorities) may be an indication that the majority of persons, except in the earlier years of life, are not hypersensitive to this particular bacterial protein, and when attacked by streptococcus they suffer only from the local inflammatory reactions, resulting in such symptoms as angina.

Smillie<sup>44</sup> cites an instance in which three little girls came together for a party. They were neither from the same home, nor school-room, and not exposed to any condition in common. At the time there was no scarlet fever in the neighborhood. Three days after the party all three developed sore throat. Two days after this one child showed a typical scarlet fever; the second had, in addition to a sore throat, a mild and questionable rash; the third child showed typical signs and symptoms of septic sore throat, but with no rash or other evidence to warrant a diagnosis of scarlet fever. From the throat cultures of all three children the hemolytic streptococcus was isolated and the three strains were exactly

alike culturally, serologically and in animal inoculations. Based on this, Smillie asks the following questions: "Were the first two children infected with something in addition to the beta-hemolytic streptococcus that produced scarlet fever in them? Is it possible that scarlet fever is due to two factors? Or did the third child really have scarlet fever without the rash?" From our standpoint the first two children were not "infected with something in addition" to the streptococcus. All three were infected with the same kind of organism, namely, the streptococcus; but two out of the three were hypersensitive (one more than the other) to streptococcus protein, while the third was not. It is not only possible, it is quite probable that scarlet fever is due to two factors: (1) Streptococcus infection, and (2) streptococcus protein intoxication. The latter will show itself only in those hypersensitive to this protein. This might explain the above described conditions of the three children.

In studies of an epidemic of scarlet fever at the Agricultural School of the University of Minnesota, in 1921, Diehl and Shepard<sup>27</sup> found that only 1 out of 66 intimately exposed persons developed the disease and that in only 15 out of a total of 59 cases of scarlet fever could definite proof of exposure to known cases be obtained. The control of this epidemic was brought about only when all persons showing "red throats" or angina were carefully isolated.

All of the above facts indicate that healthy and convalescent "carriers" of streptococci, as well as mild and missed cases of streptococcus disease may be of prime importance in the spread of scarlet fever to hypersensitive persons. Chapin<sup>28</sup> believes that the failure to properly control and prevent scarlet fever is due to the difficulty in locating and controlling "carriers" and missed cases. Chesley<sup>29</sup> emphasizes the fact that even "immunes" may be "carriers" of scarlet fever. The entire "carrier" problem, as it relates to the spread of scarlet fever, will be much simplified if our attention may be focussed on the streptococcus, and the actual prevention and control of the disease will be easier of accomplishment if we may look upon all human virulent streptococcal infections and diseases as potential sources of streptococcal protein intoxication, or so-called scarlet fever, in those who are susceptible. Based on our theory it may be said, that in isolating cases of scarlet fever to prevent the spread of the disease we have been shutting up only those poor unfortunates who are hypersensitive to streptococcus protein. What we, as physicians and health officials, should aim at is the proper isolation and treatment of *all* those individuals (personally fortunate in not being hypersensitive to streptococcus protein, but more dangerous to the public health and welfare), who have simple streptococcus infection or disease, or who are "carriers" of virulent streptococci.

In this same connection, Mironesco<sup>30</sup> is of the opinion that

scarlet fever may be spread by cases which show no sign of the disease except a sore throat. Shepard<sup>31</sup> also offers evidence to show that during an epidemic of scarlet fever which was carefully studied persons having only a mild angina apparently were the sources of typical scarlet fever in others. Laird<sup>32</sup> records a case of a hospital ward maid who recently had a sore throat, in fact, who had chronic enlargement of the tonsils and a deflected nasal septum, and who had from childhood suffered from sore throat. While her brothers and sisters had scarlet fever twelve years ago, she never showed symptoms of this disease. It was conclusively demonstrated that this ward maid—a so-called “healthy carrier”—had been the source of a recent epidemic of scarlet fever. Maclean<sup>33</sup> traced a milk-borne outbreak of scarlet fever to a milker who had a streptococcus sore throat but no evidence of true scarlet fever either before or after. On this milk route, in addition to the cases of scarlet fever, 29 cases of sore throat were discovered. These throats presented an identical appearance with those accompanied by a rash, but with milder constitutional symptoms. Johannesen<sup>34</sup> describes an instance in which a servant girl, while nursing a scarlet-fever patient, developed a mild simple tonsillitis. Three days later she returned to her home many miles away, situated in an isolated forest country. She was not ill enough to go to bed and showed no special signs of scarlet fever. She was out daily among her relatives and friends. Scarlet fever immediately became epidemic, 24 families and 67 persons out of a population of 533 persons being affected. No imported case of typical scarlet fever to cause such an epidemic was found. Each of the above described persons, although individually not hypersensitive to streptococcus protein, and hence not having scarlet fever, may have carried the streptococcus or may have been the source of streptococci carried to different groups of persons containing a certain proportion of hypersensitive individuals.

The apparently contradictory evidence as to the possibility of experimentally or artificially transferring scarlet fever from one person to another, recently summarized by Hektoen,<sup>45</sup> from the viewpoint of our theory might be explained by assuming that such results naturally would be expected to vary and even to be contradictory, depending upon the presence or absence of hypersensitiveness to streptococcus protein in persons involved in the experimental inoculations. Moreover, if streptococci remain localized in the throat or some other site, such as the uterus, and there give off their protein poison, it probably would not be possible to transmit the disease by inoculation with blood or other body fluids which might be sterile.

**B. PRACTICAL APPLICATIONS.** If scarlet fever is a manifestation of streptococcus protein hypersensitiveness it is evident that the prevention as well as the treatment must be aimed at (1) the

streptococcus in general, and (2) the hypersensitive state of the individual.

In the prevention of scarlet fever the necessity for isolation of all frank cases of the disease, as well as various other virulent streptococcus infections or diseases, has been emphasized. It is hardly necessary to suggest also that adequate, concurrent and terminal disinfection of all fomites and discharges in such diseases are of equal importance. In addition to this, the use of anti-streptococcus vaccines or sera may be logical in combating the streptococcus *per se*. However, the use of vaccines by the usual methods of dosage may be of no value in the actual control or treatment of scarlet fever for the reason that instead of combating the disease in certain susceptible persons, the disease, or hypersensitive attack, may be actually initiated or intensified. This may explain the rather contradictory results in the use of streptococcus vaccines and antisera. Better results possibly may be obtained by giving streptococcus vaccine from the standpoint of inducing a specific desensitization, that is, by very small initial doses gradually increased.

Even though living virulent streptococci may be present in the throat and tonsils, much may be done to prevent or at least to decrease the multiplication of these organisms and the absorption of streptococcus protein into the lymph and blood. Thus Milne's prophylactic, which involves the swabbing of the tonsils and pharynx with a 10 per cent solution of phenol in oil, may be of distinct value in decreasing the multiplication and autolysis of streptococci and the consequent absorption of streptococcus protein. Like results may be obtained by the use of a 1:2000 mercury perchloride throat spray as recommended by Thornton,<sup>35</sup> or a spray of pyocyanase as suggested by Sauer,<sup>47</sup> or an insufflation of sodium sozoiodolicum with sulphur as used by Rubens.<sup>48</sup> Moreover, the anatomy and pathology of the tonsils may be important in determining the reaction of the body to streptococcus protein. Bullowa<sup>36</sup> believes that the mechanical pressure action of swollen tonsils or the squeezing of large tonsils in the act of swallowing readily permits or aggravates the passage and absorption of the scarlet fever "virus" into the system. If this is true, judicious tonsillectomy may be of great value in the prophylaxis against scarlet fever. Furthermore, Bullowa recommends in the treatment of scarlet fever involving very large, inflamed tonsils that the crypts be drained and if necessary that the plica be incised to relieve pressure effects. This would be a logical treatment in the light of our theory and findings. Tonsillectomy during the course of scarlet fever probably is not always a wise procedure, as the raw, bleeding operation wound may be a means of more ready absorption of "virus," or protein, into the lymph and blood stream. In fact, cases have been seen in which much aggravation

of all scarlet fever symptoms has followed tonsillectomy during the course of the disease.

In a consideration of the possibilities for bringing about a desensitization of the person to streptococcus protein in both the prevention and treatment of scarlet fever from the standpoint of our theory, we must inquire briefly into the phenomenon of so-called antianaphylaxis. By various observers it has been found that following anaphylactic shock a refractory state is evident, that is, the animal which was previously sensitive no longer reacts in like manner to subsequent injections of the same antigen. This phenomenon, while not always permanent, is analogous in some ways to that of immunity against bacterial infection. Antianaphylaxis may be acquired either by having an anaphylactic attack or it may be induced artificially. Such induced antianaphylaxis may be divided into (1) non-specific antianaphylaxis, and (2) specific antianaphylaxis. Non-specific antianaphylaxis may be brought about by the ingestion or injection of certain drugs, foreign sera, peptone or other proteid substances. The chief drugs which have been reported to have preventive or curative influence are atropine sulphate, adrenalin, chloral hydrate and lecithin, the first two giving the most uniform results. The beneficial effects in the treatment of scarlet fever by the use of convalescent or normal whole blood or serum may be based at least partially on the production of a non-specific antianaphylaxis. The very fact that normal blood is reported by Moog<sup>49</sup> to have nearly as much therapeutic effect as blood from convalescents is an argument in favor of the non-specific nature of the protective reaction induced. Specific antianaphylaxis, according to Coca,<sup>2</sup> may be induced: (a) By desensitization with small, slowly injected doses at proper intervals of the specific antigen; (b) by antibody protection, through the re-injection of the specific antigen just before the suspected development of the hypersensitive state. Such specific desensitization is not so evident in serum allergy and other forms of allergic hypersensitiveness as in experimentally produced anaphylaxis and often is difficult to accomplish. Until some accurate method for such specific desensitization to streptococcus protein can be developed, it may be wise to depend on various methods of non-specific desensitization in the control and treatment of scarlet fever.

Auer<sup>37</sup> demonstrated that 3 mg. of atropine sulphate injected subcutaneously in guinea-pigs would save the animals from acute anaphylactic shock and death. This drug has been used with good effect in some cases of scarlet fever, and is said to lessen the susceptibility to the disease. Adrenalin is another drug which by some is considered almost a specific in the prevention or treatment of experimental anaphylactic shock. It is interesting to note that various authorities have advocated the use of adrenalin in the treatment of scarlet fever, especially in severe malignant cases

with marked depression or "shock." Thus, Hutinel<sup>38</sup> recommends the slow, intramuscular injection of a small amount of a 1:1000 solution of adrenalin in saline. In cases of scarlet fever with sudden collapse, Meara<sup>39</sup> suggests the use of adrenalin by the skin in a dose of 10 drops of a 1:1000 solution, slightly less by the muscle, and 2 to 3 drops by the vein in adults. For a child of five years he uses one-quarter the above doses, and for a child of ten to twelve years one-half the above doses. Meara believes the action is most certain when the drug is given by the vein. He wisely cautions against the careless use of adrenalin on account of its rapid action on the blood-pressure and heart. Rolleston,<sup>40</sup> as well as Kramer,<sup>41</sup> also have noted good results in the treatment of scarlet fever by the judicious use of adrenalin.

One of the chief non-specific antianaphylactogens is peptone. In 0.4 to 0.5-gm. doses by mouth this protein may act as a desensitizing agent and apparently is polyvalent for most of the proteins causing hypersensitiveness. Peptone may be given by mouth or be injected subcutaneously or intramuscularly. In an account of peptone therapy, Fatou<sup>42</sup> indicates that he has obtained excellent results in the treatment of various hypersensitive conditions by the administration of 0.5 gm. of peptone one hour before each meal by mouth. This may be administered three times a day for a week then suspended for a week, or it may be given rather continuously. It is necessary that peptone for therapeutic purposes shall be of good quality. As Auld<sup>43</sup> has shown, if peptone contains histamine very severe and troublesome reactions may occur. The administration of pure peptone by mouth gives rise to little or no reaction, while in some instances it has resulted in very severe reactions when given subcutaneously, intramuscularly or intravenously. Even such intense reactions often have been followed by excellent therapeutic results.

With the above facts in mind, it would be of interest from the viewpoint of our theory to test the results of peptone therapy in scarlet fever; also to test its possible prophylactic power in protecting contacts from attacks of the disease. If positive results should be obtained it would lend therapeutic confirmation to our hypothesis, and be an important step in the prevention and treatment of scarlet fever. This will form the basis of a future communication.

**VI. Summary.** 1. Based on original observations made during the last fifteen years, an attempt is made in the first part of the present study to demonstrate the almost complete uniformity in the clinical signs and symptoms of drug allergy, serum allergy and scarlet fever.

2. Based largely on the investigations of other observers, it is emphasized in this study that virulent hemolytic streptococci are

present, frequently in pure culture, in practically 100 per cent of scarlet fever throats, and that they are neither so generally present, nor in such enormous numbers in other diseases or normal throats; moreover, streptococci frequently have been found in the blood and complicating lesions of scarlet fever, and for many years have been suspected of having an etiological relation to this disease.

3. By the use of cutaneous protein sensitization tests it is demonstrated in the experimental part of this study that various apparently normal individuals who have had scarlet fever in the past or who never have had the disease show from 41 to 61 per cent of positive reactions when tested with streptococcus protein. On the other hand, cutaneous tests with streptococcus protein on individuals during the active course of scarlet fever, particularly in the early stages, are found to be uniformly negative. From this it may be concluded that while a fair proportion of normal persons are hypersensitive to this particular bacterial protein, individuals with active cases of scarlet fever apparently are in a state of desensitization.

4. It is suggested, therefore: (a) That scarlet fever is a reaction of specific hypersensitiveness to streptococcus protein; (b) that scarlet fever is a compound condition, involving primarily a local streptococcic infection (usually of the throat, but frequently of an accidental or operative wound, burns or associated with the puerperium); and secondarily, a streptococcus protein intoxication in those who are hypersensitive.

5. On the basis of such a theory, it seems probable that the prevention and treatment of scarlet fever also may depend on two factors: (a) The control of the streptococcus *per se* through adequate isolation and concurrent and terminal disinfection of all cases, including not only frank scarlet fever but also all other virulent streptococcus diseases; as well as the isolation and treatment of all streptococcus "carriers," and proper attention to milk and other possible vehicles of streptococcic infection. (b) The desensitization of individuals who by cutaneous tests are shown to be hypersensitive to streptococcus protein, either by specific (vaccines or antisera) or non-specific (protein or serum) methods of treatment; and adequate attention to local sites of streptococcic infection, such as the throat, to reduce to a minimum the possible absorption of streptococcus protein.\*

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## MODERN METHODS OF TREATING LOBAR PNEUMONIA.\*

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To confine one's entire attention to the newer methods of treating lobar pneumonia would be to neglect the still most important aspects of the therapy of the disease. It is only necessary to look back over the almost countless list of discarded therapeutic measures to convince ourselves of the wisdom of the remark made by Juergensen, "Nature cures, and the only duty of the physician is to maintain life until this cure is effected."

Of late years the increase in knowledge of the etiological agents responsible for lobar pneumonia has led to an increased activity among therapeutists to develop specific forms of treatment. Specific sera, vaccines and chemicals all have their advocates and it is to these measures that we shall return after a brief consideration of the most important general methods.

**General Regimen in the Care of Pneumonia.** The toxemia of lobar pneumonia is of a sharp, sudden, severe type seen in few other diseases. Lasting, as it ordinarily does, only about seven days, the necessity of building up the body tissues is not an important one. We must do nothing to interfere with elimination (by stopping up the bowels); otherwise we may feed as we like. On the other hand it is essential to increase every form of elimination possible and to this end fluid forced to 3 to 4000 cc daily, allows the kidneys, bowels and skin to function best in this respect. Should vomiting or delirium interfere with the fluid intake subcutaneous injections of salt solution or Murphy drips may be resorted to.

The severity of the toxemia is frequently revealed by a failing myocardium. We must spare no effort to relieve the heart muscle from the very onset of the disease. Of great importance in this respect, is the prevention of any movement on the part of the patient. This, in my opinion, is the most valuable contribution that can be made by the trained nurse. The patient must be lifted whenever he even so much as turns in bed. I know of four patients who have died while, or immediately after, using a bedpan. The physician should make this clear not only to the nurse but also to the patient, care being used, of course, not to alarm the latter unnecessarily. All forms of treatment which require exertion on the part of the patient must, therefore, be modified. Recent studies by Levy have shown that the digitalized heart does not dilate as readily during pneumonia as the undigitalized controls. This would seem to be sound argument for the early administration

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of digitalis. Certain it is, however, that digitalis in some form is urgently indicated at the first sign of myocardial insufficiency. The powdered leaves may be used by mouth but a more rapid and certain method of administration is digitalin or digifoline hypodermically. Sudden heart failure may require, in addition, the use of morphine and atropine or even venesection. Caffein (sodio-benzoate) and camphor (in oil) are stimulants to be used when necessary after the full amount of digitalis has been given or when additional stimulation is required.

The toxemia may also make itself felt on the peripheral circulation in the form of vasomotor paralysis and this is best combated, or rather best prevented, by hydrotherapy in the form of cold sponging every three or four hours. As cautioned before it is ill advised to move the patient and so the sponging may be confined to the anterior surface of the body and the extremities. Moving the patient into a tub is absolutely contraindicated. Epinephrin or pituitrin are sometimes helpful in raising the blood-pressure by action on the peripheral vessels and strychnine may act by stimulating the medullary center.

Perhaps the commonest result of the severe toxemia is abdominal distention due to paralysis of the intestinal musculature. Few cases run the course of lobar pneumonia without at some time being disturbed by tympanitis and it should be anticipated and treatment instituted at the earliest moment. Turpentine stupes are often sufficient to relieve slight degrees of distention (hot turpentine stupes to be applied for twenty minutes and then replaced by hot-water stupes for twenty minutes and then the process repeated) especially if a rectal tube be inserted. More marked or persistent distention may require turpentine enemata (turpentine, 15 cc to 1000 cc of water) or glycerin enemata (glycerin, 120 cc followed by water 60 cc injected high in the bowel), and if these fail pituitrin 1 cc hypodermically, repeated in a half hour, may prove efficacious. Elimination of milk from the diet may be necessary as well. When the patient is first seen he should be given a cathartic if none has already been taken and this should be followed the next morning by a saline purgative. After this enemata may be relied on to cleanse the bowel every second day inasmuch as the diet contains very little residue.

Pain is one of the very troublesome symptoms in some cases. It is produced by the pleurisy which accompanies the pneumonitis and is the cause for the rapid and shallow breathing so often seen in the early stages of the disease. Morphine is often required to quiet this pain but it is advisable to use as small a dose as possible on account of the paralyzing action which morphine exerts on the intestinal wall. Enough relief may be gained from  $\frac{1}{16}$  or  $\frac{1}{12}$  of a grain to enable the patient to fall off to sleep and this dose may with absolute safety be repeated often. Before

morphine is resorted to an ice-bag should be tried and if this is found unavailing a tight chest swathe applied. The non-productive coughing should be stopped by heroin (easily given in lozenges containing heroin, gr.  $\frac{1}{12}$ ).

Delirium must be controlled and if morphine alone fails Schlesinger's solution may exert a quieting effect. Occasionally its effect is just the opposite and it serves only to increase the restlessness.

If cyanosis and dyspnea become prominent symptoms great relief may sometimes be had from the administration of oxygen. This is best done in a suitable oxygen chamber but quite satisfactory results can be obtained by bulbing the oxygen through a water jar and into a soft-rubber catheter which has been introduced through the nose to a point where its tip is just visible back of the soft palate. This method is less disturbing to the patient than the funnel and is also more easily performed by the attendant. Fresh, cool air is most comforting to the patient and aids in reducing any restlessness. Exposure should be avoided.

**Doctor's Orders.** Absolute rest (give details).

Force fluids to 3000 cc.

Soapsuds enema every two days if necessary.

Cold sponging if necessary for temperature over 103° F. every three hours without moving patient.

Ice-bag to head or chest for pain.

Chest swathe for pain when needed.

Morphine, gr.  $\frac{1}{12}$  (hypodermically) for pain if necessary; repeat in one hour if necessary.

Turpentine stupes if necessary for distention.

Digitan, gr.  $1\frac{1}{2}$ , every four hours for 12 doses.

**Specific Therapy.** SERUM. Horse (Cole *et al.*)

Antibody extract (Huntoon).

Chicken (Kyes).

Convalescent human serum (Stengel).

VACCINE. Prophylactic (Austin and Cecil).

Therapeutic (Rosenow).

CHEMICAL. Quinine.

Numoquin (Optochin).

Alkaline.

Of the eight kinds of specific therapy charted above the Type I pneumococcus serum developed by the Rockefeller Institute workers is the only one that has received enough of a trial to warrant analytical discussion.

Kyes' chicken serum (prepared by further immunizing the already immune chicken to the various types of pneumococcus) has been used in Chicago in the Cook County Hospital and also

tried at Camp Grant. The statistics relative to the case mortality are suggestive (a reduction from 45.3 per cent to 20.8 per cent in the Cook County Hospital, and a mortality of 7.7 per cent in 322 treated cases at Camp Grant) but the reactions following its use coupled with other reasons led to modifications and I have seen no further statistics.

An attempt to use therapeutically the immune serum obtained from convalescent pneumonia patients by bleeding them soon after their crisis was made in Philadelphia by Dr. Stengel and reported last year. This method is not only attended by great technical difficulties but is also open to many theoretical objections. The chief objection is that serum from convalescent patients is never found to be as rich in specific antibodies as is the serum produced by animal immunization, and treatment with this latter form of serum has already been discarded as useless in all types except Type I. (I allude of course to serum from animals immunized to Types II, III and IV pneumococcus.)

Prophylactic vaccination with killed cultures of Type I, II, III, pneumococcus was performed by Austin and Cecil on 12,519 soldiers at Camp Upton. During a comparatively short period of observation the control group showed many more pneumonia cases, and, more upper respiratory infections as well, than did the vaccinated group, and it was noted that what cases did occur were of a very much milder form. We can hardly all of us be vaccinated every November but in suitable cases this form of treatment may be of real service.

Rosenow developed a partially autolyzed vaccine with which he treated cases of pneumonia. Little is known as to the variety of cases treated but his mortality in a group of 200 cases was as low as 7 per cent. This method has not met with general acceptance and it has not been given a sufficient test so that we must pass it by with a mere mention.

Of the drugs which from time to time have been advocated quinine has recently returned to prominence as a specific in pneumonia. Many years ago it was used very frequently as an antipyretic and therefore often in pneumonia. In 1911, Morgenroth and Levy announced the discovery of a quinine salt which they called optochin. In the test tube this drug was found to have an almost unbelievable power to kill the pneumococcus. No very extensive therapeutic tests were made in this country as it was soon learned that occasional toxic manifestations were accompanied by lesions in the optic nerve. In Germany, however, a basic salt has recently been prepared which is said to be harmless and at the same time very efficacious in the treatment of lobar pneumonia. This substance is known as numoquin. It is brought to your attention now because the writer believes that when sufficient knowledge about its use is obtained we shall have a most valuable adjunct to

our armamentarium. Until that time however we may, if desired, safely turn to quinine which is said by some writers (Cohn-Bronner) to surpass optochin. Painful local reactions usually follow the hypodermic injection of quinine so that a high dilution is necessary. One satisfactory preparation which may be obtained at any drug store is:

R—Quinine muriate . . . . .	2.0
Urethane . . . . .	1.0
Aqua dist. . . . .	q. s. ad 20.0
Sig.—5 cc intramuscularly—repeat in twenty-four hours and again forty-eight hours later if necessary.	

Alkaline treatment has been advocated by many clinicians but the most thorough study of this phase of the condition (made by Means) has demonstrated that not every case suffers from an acidosis. Means points out that the production of an alkalosis not only may readily occur but also is quite dangerous. To avoid this it is necessary to make frequent observations on the alveolar air and the blood  $\text{CO}_2$ . This fact complicates the procedure to such an extent as to make it inapplicable for general routine use.

The form of specific therapy with which the writer has had most experience is Type I antipneumococcus serum. During the War he was stationed for three months at the Rockefeller Institute Hospital and from there sent to Camp Meade to treat the pneumonia cases. The first winter there (1917 to 1918) the writer personally treated 50 cases of Type I pneumonia with serum obtained from Mulford.

TABLE I.—TYPE I, LOBAR PNEUMONIA (CAMP MEADE)

	Number.	Died.	Mortality, per cent
Treated . . . . .	50	3	6.
Untreated . . . . .	7	0	0.
Total . . . . .	57	3	5.3

It will be noted from Table I that only 3 cases died and it should be added that 1 of these 3 was treated first on the sixth day of the illness having been brought in moribund; 1 had a tuberculous cavity which practically involved the whole left upper lobe, and the third, though operated on by mistake for a suspected empyema before being seen by our service, was apparently cured of the pneumonia only to die ten days later from a meningitis. In the treated group there were no complications other than those mentioned above. There was unfortunately no control group.

Two years later while resident at the Boston City Hospital, the writer supervised the treatment of 75 cases of Type I pneumonia with serum obtained from the Massachusetts Board of Health. The cases comprised men and women of all ages and varieties of physical condition, admitted, many of them, late in the disease. The

mortality rate in this group of cases was 17.3 per cent. Of these cases (56 cases) which were treated during the first week of the disease only 7 died, giving a mortality of 12.5 per cent.

During the next two years, under Dr. E. A. Locke's direction, every serum treated case was controlled by a similar untreated case. The controls were made to compare clinically as nearly as possible to the treated group. It will be seen from the Table (II) that the mortality in each group was about 17 per cent.

TABLE II.—MORTALITY, RATE, 145 TREATED: 71 CONTROL CASES (BOSTON CITY HOSPITAL).

	Number cases.	Number deaths.	Mortality, per cent.
Group A . . . . .	75	13	17.3
Group B . . . . .	70	12	17.1
Totals . . . . .	145	25	17.2
Control Group B . . . . .	71.	12	16.9

In a recent address delivered before the New York Academy of Medicine, Dr. Locke carefully analyzed the serum treatment of pneumonia and brought out, among many interesting points, the fact that the average mortality obtained in 6 civilian hospitals in Boston, New York and Baltimore was 19.3 per cent. From 11 Base Hospitals in the various army camps, however, an average mortality of 9.5 per cent was obtained, and the Rockefeller Institute Hospital figures show 195 cases treated with a mortality of 9.2 per cent. These statistics seem to show that, although serum treatment of Type I lobar pneumonia is of definite value in reducing the case mortality, it is a procedure which requires exceptional facilities and the service of highly trained specialists.

Cecil at the Bellevue Hospital, and Connor at the New York Hospital, have for the past few years given a thorough trial to a new form of treatment. This consists of the administration of a polyvalent antibody extract prepared by Huntoon of the Mulford Laboratories from horse serum which has been highly immunized against the fixed types of pneumococcus (Types I, II and III). This preparation is a protein-free suspension of specific antibodies in salt solution. The results from treatment with this preparation obtained at the Bellevue Hospital are summarized in Table III.

Dr. Cecil, who has very kindly loaned the writer some of his lantern slides, asks that it be made clear that the intravenous injection of this substance late in the disease is attended by many severe reactions which, in a few instances, have terminated fatally. For this reason subcutaneous injection of larger amounts is now being tried and the results will soon be announced. Both Dr. Cecil and Dr. Connor feel encouraged to go on with this work on account of the very definite indication of the value of the method. If circum-

stances are favorable this preparation will soon be available for general use.

TABLE III.—COMPARISON OF DEATH-RATE IN TREATED AND CONTROL SERIES

Antibody Wards:				Control Wards:			
Type.	Cases.	Deaths.	Rate, per cent.	Type.	Cases.	Deaths.	Rate, per cent.
Pn. I . .	158	21	13.3	Pn. I . .	162	36	22.2
Pn. II . .	83	23	27.7	Pn. II . .	67	27	40.3
Pn. III . .	73	29	39.7	Pn. III . .	60	24	40.0
Pn. IV . .	110	18	16.4	Pn. IV . .	121	29	24.0
Total	424	91	21.4	Total	410	116	28.3
Strept., etc.	48	24	50.0	Strept. etc.	35	12	34.3
Unclass. .	36	14	38.8	Unclass. .	47	20	42.5
Gr. tot. 508		129	25.3	Gr. tot. 492		148	30.0

**Summary.** 1. We must never lose sight of the importance of general therapeutic measures in the treatment of lobar pneumonia.

2. Of the special measures Type I antipneumococcus serum is the only one which has given satisfactory results in a large enough series to warrant its further use.

3. Quinine therapy seems very promising and may subsequently prove to be of great value.

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## THE IMPORTANCE OF ATAVISM IN THE DIAGNOSIS OF HEREDITARY HEMORRHAGIC TELANGIECTASIA.

RATIONALE OF TREATMENT AND REPORT OF AN ADDITIONAL FAMILY.

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CLINICAL interest in hereditary hemorrhagic telangiectasia dates from the paper of Sir William Osler,<sup>4</sup> in 1901. Rendu,<sup>3</sup> however, in 1896, was first to associate familial epistaxis with the multiple telangiectases that together constitute the chief features of this pathological entity. It may be defined as an hereditary abnormality characterized by the formation of localized dilatations of capillaries and venules which occur chiefly in the skin of the face and in the mucosa of the nose and mouth and which may give rise to apparently spontaneous hemorrhages, most commonly in the form of recurrent epistaxis.

Among 30 families affected with this disease which are reported in the literature, there are found 57 undoubted and fully detailed cases and 155 other probable cases which are only incidentally mentioned. In addition to these 212 cases occurring in 30 clearly affected families there have been reported a number of isolated, apparently non-hereditary cases which conform so closely to the disease under consideration that one is forced to class them in the same group. For purposes of analysis in this article, however, only the 57 fully reported cases are utilized. A chronologically arranged bibliography is appended.

Analysis of the reports in the literature seems to justify the conclusion that atavism has been overlooked as a factor in the heredity of this disease. Furthermore there are certain misconceptions regarding the mechanism of the hemorrhages. The purpose of the present article is to discuss these two factors and to point out their importance respectively in the diagnosis and treatment of the disease.

The appended detailed case report may serve in lieu of formal review of this somewhat unusual condition.

**Atavism.** It is commonly believed that there are no "skipped generations" in the inheritance of this disease. The best review of the subject is that of Steiner.<sup>21</sup> His diagrams show clearly that there are instances of atavism among the families reported by him as well as among those of older authors reviewed in his paper. But he makes no mention of this factor and has apparently missed its significance. Goldstein,<sup>24</sup> in a recent extensive review, epitomizes a

number of the isolated, apparently non-hereditary cases previously alluded to. He also fails to recognize the factor of atavism in the classical cases and accordingly fails to realize that most of his "non-hereditary" cases should properly be regarded as atavistic instances of hereditary telangiectasia. A review of most of the recent textbooks and systems of medicine shows that this factor is not generally recognized—the only mention at all concerning it being that of Stevens,\* who states that the disease "shows little atavistic tendency."

I find seven clear instances of atavism in four of the thirty families reported as exhibiting the disease in classical form:

Osler's<sup>4</sup> first patient, "George B," had a grandniece, granddaughter of "the patient's elder sister who was herself afflicted with the disease." This grandniece "had frequent epistaxis." "None of his (George B.'s) nephews or nieces have bled." Therefore, from a clinical standpoint at least, the mother of this "grandniece" was free of the disease yet transmitted it to her daughter.

Steiner's<sup>21</sup> first two families show most interesting examples of atavism. In his first family there are two instances of atavistic transmission (one by female and the other by male, neither of whom showed signs of the disease) to their respective offspring. His second family comprised patients in the second and third generations of a family whose "first generation" showed no evidence of the disease. Moreover the afflicted individual in the third generation came of a non-affected parent of the second generation, so that this case harks back to some ancestor at least two generations removed.

Audry's<sup>23</sup> family of four affected generations "started" from apparently non-affected grandparents although on one side of this non-affected pair were two affected members in the same generation.

Weber's<sup>8</sup> family showed a patient in the fourth generation whose taint was transmitted through the father (himself free of symptoms) from an afflicted grandmother in the second generation.

Of course it may be that the non-affected "carriers" of this hereditary abnormality are merely clinically free of symptoms and on careful examination might show some of the minute vascular defects that characterize the disease. But this is beside the point. Practically speaking we have to admit 7 clear cases of atavistic inheritance among 212 cases mentioned in the literature. Moreover, one of these skipped two and possibly more generations. It would not be surprising then that many other like sufferers might well be unaware of the occurrence of nose-bleeding or telangiectases in their ancestors. A situation analogous to this occurred in one of Osler's cases which was at first not accepted as an authentic example of the disease because the patient knew of no afflicted relatives. "Later," as Steiner remarks, "another member of the family, similarly affected, was discovered."

\* Practice of Medicine, Philadelphia, 1922, p. 718.

In the light of such cases as these we are forced to recognize a number of others reported in the literature under various names (but heretofore excluded from this pathological entity) as, most certainly, atavistic examples of hereditary hemorrhagic telangiectasia. A bibliography of such cases is also appended, although it is probably by no means complete.

**Diagnosis.** The presence of a typical family history makes the diagnosis easy in many instances. But a review of the errors in diagnosis that have been recorded shows that this does not always obtain. Seven cases were thought to be examples of hemophilia by the authors reporting them (Legg,<sup>1</sup> Rendu,<sup>3</sup> Chiari,<sup>2</sup> Coe<sup>26</sup>). This mistake would hardly be made at the present time, for the line of hereditary and sex incidence are entirely different and in hemophilia there is greatly prolonged coagulation time together with a tendency to bleed unduly from slight traumatism of normal tissue, both of which are absent in this disease. The patient reported by Hutchinson<sup>19</sup> had previously been treated for pernicious anemia. One of Steiner's<sup>21</sup> patients had had a small lesion excised from the tongue as a carcinoma which in all probability was simply a telangiectatic spot.

The author's patient had been previously diagnosed "chronic purpura hemorrhagica." This error would have been rendered unlikely by the proper evaluation of the family history and would have been avoided entirely by the simple test of pressing a glass slide against the purpuric-like lesions. Telangiectases of the sort found in this disease disappear under sufficient pressure while purpuric spots do not. The latter are fugacious while telangiectases are more permanent. There are only three instances recorded in which some of the telangiectases disappeared spontaneously. In purpura hemorrhagica the blood platelets are usually greatly reduced; they are apparently normal in hereditary hemorrhagic telangiectasia.

Finally, in all cases of obscure hemorrhage this disease must be borne in mind; and here it is that the role of atavism becomes one of major importance.

The absence of characteristic family history does not exclude the possibility of this disease.

Judging from Osler's<sup>4</sup> patient who came to autopsy and from the history of Richardson's<sup>20</sup> patient, gastro-enteric hemorrhages might well be the leading symptom in a given individual.

A brother of the author's patient died of "hemorrhages from the throat" which were said to be due to tuberculosis but which in all probability were from pharyngeal telangiectases.

Neurologists have reported a number of cases of cortical angiomata causing epileptic and hemiplegic symptoms. Goldstein's<sup>24</sup> patient had hemiplegia at forty years of age without any evidence of lues, hypertension, cardio-renal disease or arteriosclerosis. He attributes this to rupture of cortical telangiectases.

Several of the patients reported have had metrorrhagia and menorrhagia without any obvious cause, indicating the probability of telangiectases in the mucosa of the birth canal.

None of the classical cases has exhibited hematuria or other evidence of telangiectases in the urinary tract. Nevertheless it is interesting to speculate as to the possible relationship of this disease to certain cases of so-called "essential hematuria." Urologists have reported a number of such found at operation to be caused by small varices and angiomas of the renal pelvis. Particularly suggestive is the group of "hereditary hematuria" cases reported by Pearson,<sup>39</sup> Aitken<sup>38</sup> and others. The hereditary tendency recorded in these is identical with that of the disease under consideration, both sexes transmitting the disease and both being equally affected. No mention however, is made of telangiectatic lesions or of epistaxis in these individuals so that as far as the records go the analogy is incomplete.

**Prognosis.** The prognosis of this disease is sufficiently grave to demand our best therapeutic efforts. Although the outlook, *ad vitam*, is good, the prospects *ad valitudinem*, are decidedly poor. The majority of these patients at the time of their reports (average age forty-two) were semi-invalids. The hemorrhages tend to increase in frequency and severity as middle life is reached, and the nervous and physical strain of these repeated losses of blood make the plight of these unfortunate individuals very miserable indeed. A few however have not been incapacitated.

Of the 57 reported patients, only 1 died of the disease itself (Kelly's<sup>6</sup> patient, who died of epistaxis at the age of forty-eight years). Of the 155 additional patients mentioned, 5 died of epistaxis (average age forty-five years), 1 died of convulsions presumably from cerebral hemorrhage at the age of three years, and 1 died of "hemorrhages from the mouth" as did also the brother of the author's patient. Thus 8 of 812 (approximately 4 per cent) died of the disease itself. A "follow-up" of the others would probably show the majority dead long before their time, due to intercurrent maladies dependent upon their weakened condition.

**Mechanism of the Hemorrhages.** The hemorrhages constitute the only important therapeutic indication in this disease, except possibly the cosmetic features incident to the telangiectases themselves. The mechanism of these hemorrhages has been explained in two different ways: One hypothesis postulates some underlying hemorrhagic diathesis or blood dyscrasia as the determining factor. The other maintains that the telangiectases are primary and that the hemorrhages are mechanical by-products resulting from the rupture of these vascular defects.

Steiner,<sup>21</sup> it would seem, adheres to the "hemorrhagic diathesis" view although he does not use the phrase and seems to disregard his theory in consideration of treatment. He says "the bleeding

in these cases is often so severe that a condition of marked anemia is induced which may be an important factor in the development of the telangiectases. Certain it is that bleeding generally precedes the formation of these . . . and may do so with many years intervening." The inference from the above is that Steiner regards the hemorrhages as primary (due to hemorrhagic diathesis) and the telangiectases secondary thereto.

The author is convinced of the contrary. Bleeding does not precede the formation of telangiectases although bleeding may, and usually does, precede their discovery. All the evidence points to the probability of an early and prior age of formation of the intranasal lesions in patients exhibiting early epistaxis. Perhaps Steiner means simply that *additional* telangiectases are caused by the anemia.

The "chief complaint" in 40 of the 57 patients (70 per cent) is recurrent epistaxis since childhood. Telangiectases, however, are not discovered as a rule until adult life is reached. For, in the first place, these lesions do not appear on the face and other cutaneous surfaces until after twenty years of age in most instances. Why this is we do not know. In the second place, these patients, although exhibiting epistaxis since childhood, apparently do not consult physicians until adult life is reached when secondary constitutional symptoms drive them to seek help. The significant fact here, however, is that every one of the few juvenile subjects examined by rhinoscopy showed intranasal lesions. Furthermore in practically every reported patient exhibiting epistaxis who was subjected to rhinoscopy (44 of the 57) telangiectases were found. Judging from these facts we conclude that the formation of intranasal lesions is the earliest manifestation of the disease in all patients exhibiting initial epistaxis.

The mechanistic hypothesis of the hemorrhages is further strengthened by the following considerations: No patient suffering from this disease in classical form\* has bled abnormally from trauma other than from traumatized telangiectases. None has had spontaneous bleeding of any sort other than from obvious or presumable telangiectases (excluding hemorrhoids). By "presumable telangiectases" are meant such instances as the following: the patient of Richardson's<sup>20</sup> that had melena and became sallow and weak before epistaxis appeared or spots were noted, caused (as the autopsy of Osler's patient would lead us to presume) by preformed telangiectases in the gastro-intestinal tract: or the author's patient who had metrorrhagia and menorrhagia at intervals from puberty until her first pregnancy due, presumably, to telangiectases in the birth canal which were wiped out during labor, as she had very little of this form of bleeding afterward.

\* Legg's patient is an apparent exception, subject, however, to other explanation than that given in the report.

Blood studies by most authors have revealed no abnormality except secondary anemia. Blood coagulation time is normal in uncomplicated cases\*—as shown in the reports of Osler,<sup>4</sup> Hutchinson and Oliver,<sup>19</sup> Goldstein,<sup>24</sup> Hanes,<sup>13</sup> Steiner,<sup>21</sup> Richardson<sup>20</sup> and the author. The blood platelets are normal (Steiner and the author).

On the basis of the foregoing facts we may conclude that the hemorrhages are the result of rupture of the thin-walled, superficial vascular defects that characterize the disease. This rupture may be brought about in a variety of ways—slight traumatism, insignificant irritations, vasomotor or mechanical congestion. It is suggestive that 8 patients are recorded as awaking frequently at night to find the pillow wet with blood from epistaxis. The intranasal congestion which probably occurs during sleep, doubtless determines telangiectatic rupture in such instances.

**Treatment.** The treatment of the disease has been very unsatisfactory, due, according to the author's opinion, in some instances to lack of faith in the purely mechanistic cause of the hemorrhages and in others to lack of zeal in pushing this conception to its ultimate therapeutic conclusion.

Only 2 therapeutic clinical cures are recorded, 1 by Hutchinson and Oliver<sup>19</sup> and 1 by Chiari<sup>2</sup> both of whom destroyed their patients' offending lesions by thermal cautery. Most modern authors recommend similar local treatment but none seems to have emphasized its all-important features.

My opinion is that a painstaking, methodical destruction of all bleeding telangiectases, by thermal or chemical cauterization, under local or general anesthesia, will result in clinical cure of most of these patients. Lesions of the skin, lips and tongue are most thoroughly and permanently destroyed by the electric needle (diathermy). The difficulty lies chiefly in the cure of epistaxis. Here the assistance of a patient, skilful rhinologist is of great importance. The exact location of intranasal lesions must first be determined. Then begins the task of thorough cauterization. For this purpose the best seems to be the chromic acid crystal, fused on the tip of a metal applicator and touched directly against the lesion to be destroyed. The same lesion may require several applications before it disappears entirely. Not more than two or three lesions should be cauterized at one sitting. Cocainization of the mucosa is sufficient anesthesia for this. In a difficult case where for anatomical reasons the offending spot cannot be reached, more radical measures must be employed, such as submucous resection of the nasal septum or removal of all or part of a turbinate body with a view either to remove thereby the bleeding lesion or to gain better access to it for cauterization. The danger of producing rhinitis sicca must be

\* Freudenthal<sup>23</sup> has recently reported an apparent exception. His patient is said to have had a coagulation time of sixteen minutes which, it is stated, was rapidly reduced to two minutes by several intravenous injections of sodium citrate.

borne in mind throughout, but in a severe case this possibility should not make the operator too conservative. Intranasal manipulations may for a time increase the tendency to epistaxis but once the offending lesion or lesions have been located they can be destroyed. This should be the goal of both patient and operator.

Needless to say, nothing of decisive value can be done for such rare cases as the one of Osler's with lesions in the stomach or that of Goldstein's with cortical telangiectases. Metrorrhagia caused by telangiectases might however be amenable to local treatment. The hemorrhages themselves require the usual emergency treatment, whether it be for epistaxis or bleeding lip or tongue. Measures designed to influence coagulation time of blood are of no value.

**CASE REPORT.**—Mrs. M. C., aged thirty-seven years, a Russian Jewess, was admitted to the Woman's Medical Ward, on the service of Dr. Alfred Stengel, July 1, 1922. She was referred with diagnosis of "chronic purpura hemorrhagica," for which she had been given calcium lactate internally and thromboplastin by hypodermic injection over a period of many months without improvement.

*Chief Complaint.* Nose-bleeds, spots on lips and tongue, weakness, and swelling of the feet.

*History of Present Illness.* The patient has had occasional epistaxis as far back as she can remember but until three or four years ago the attacks were infrequent and easily controlled. Since this time however they have increased greatly in frequency and severity—averaging one a week and sometimes she has had daily attacks for a week or more at a time. The epistaxis seems to be chiefly left sided and is frequently nocturnal in occurrence. She is now very weak and nervous, has lost 15 pounds in eight months and has palpitation and dyspnea on slight exertion in addition to headache, vertigo and some edema of ankles.

Three years ago she had the first attack of bleeding from her tongue. She consulted a doctor who called her attention to small purplish spots on her tongue and lips. She had never noted any of these before. Two years ago she found that similar spots were appearing on her forearms and fingers. There have never been any spots on the face, trunk or lower extremities. All the spots have remained unchanged.

In addition to epistaxis she has had four attacks of moderate bleeding from the tongue, and from puberty at fourteen years of age until marriage at seventeen she had considerable metrorrhagia and menorrhagia. Since her first pregnancy, however, she has had very little of this form of hemorrhage and has passed through five uneventful labors. She has had no hemoptysis, no hematemesis, no hematuria, no melena and she does not bleed abnormally from trauma. No painful swelling of joints. No abdominal cramps. No glandular swellings. No itching of skin. No jaundice. Appetite

fair. Some heartburn after eating. No vomiting. No hemorrhoids. No dysuria. No nocturia.

*Past Medical History.* Negative.

*Family History.* Patient is mother of five children living and well, except that one (her nine year old son) has frequent nose-bleed. The patient has one sister and one brother in Russia of whom she knows nothing. She lost one brother who died of "tuberculous hemorrhages from the throat." He, too had spots on his lips. The patient's mother died of "heart disease" at the age of forty-three years, and she had frequent epistaxis and spots on her face and forearms. One brother and one sister of the patient's mother also had frequent epistaxis, and the patient recalls having heard that her maternal grandfather had the same trouble.

*Physical Examination.* Blood-pressure, 115-75; temperature, pulse, respirations are normal. The patient is a fairly well-nourished white woman, aged about thirty-five years. She is pallid and of sallow complexion. Speech, mentality, station, gait and bodily movements normal.

*Head.* Rhinoscopy reveals old blood clot in left lower fossa. Both lower turbinates congested. The left side of the nasal septum presents a single dilated venule and several minute red spots which blanch on pressure. Similar spots are seen in the mucosa of both inferior turbinates.

*Ears.* Negative; no spots on tympanic membranes.

*Mouth.* The lips and tongue present similar spots, some of which are raised papules, and all of which disappear under pressure of a glass slide. Pharynx negative.

*Eyes.* Negative; no conjunctival telangiectases; eye grounds normal; marked hyperopia with astigmatism.

*Neck.* Negative.

*Thorax.* Negative. Heart and lungs normal. No spots on trunk.

*Abdomen.* Negative except that both kidneys and the sharp, non-tender edge of the spleen can be readily palpated on deep inspiration.

*Upper Extremities.* Negative except for a few small macular and papular telangiectases in the skin of forearms and fingers.

*Lower Extremities.* No telangiectases; slight edema of ankles and varicose veins under right knee.

*Neurological Examination.* Negative.

*Pelvic Examination.* Negative; cervix and vagina show no telangiectases. Uterus and adnexa normal. No intra-uterine bleeding on passage of a sound.

*Blood Count.* July 2, 1922. Erythrocytes, 4,000,000; hemoglobin, 75 per cent; leukocytes, 7000; neutrophils, 65 per cent; lymphocytes, 27 per cent; large mononuclears, 2 per cent; transitionals, 4 per cent; eosinophils, 2 per cent. No myelocytes. No abnormal changes in the erythrocytes.



Urinalysis entirely normal; acid; specific gravity, 1025.

Bleeding time, one minute; coagulation time, five minutes (capillary); six minutes (Bogg's).

Fragility test: Hemolysis begins at 0.425—complete 0.325.

Blood platelets varied from 112,000 to 280,000.

Blood Wassermann negative.

**Clinical Notes.** July 5, 1922. Had slight bleeding from mouth which patient thought was from her gums but on examination was found to come from telangiectatic spot on right margin of tongue.

July 6, 1922. Dr. H. K. Pancoast destroyed the more prominent lesions of tongue and lips with electric desiccator needle using cocaine anesthesia locally.

July 10, 1922. Treatment of intranasal lesions by chromic acid cauterization begun by Dr. David Husik.

July 12, 1922. Epistaxis last night—controlled with difficulty by packing soaked in thromboplastin.

July 14, 1922. The patient's nine year' old son reported for examination. He has a dilated venule in septal mucosa on left side and a typical telangiectatic spot on upper lip and one on left forearm. No spots on tongue. Spleen not palpable. Hemoglobin, 85 per cent. Platelets, 150,000. He has had frequent nocturnal epistaxis since age of two years.

July 18, 1922. Patient discharged. To continue treatment in nose and throat dispensary.

August 11, 1922. Readmitted. Patient did not report for treatments owing to illness in her family. Has had considerable epistaxis and is weak and nervous. "Rest cure" in ward for a few days. Has had no recurrence of lingual bleeding since desiccation of the lingual spots, which show no evidence of recurrence.

October 15, 1922. Patient has been reporting regularly to Dr. Husik for past few weeks. He has destroyed all visible lesions in left nostril. No epistaxis for two weeks.

December 10, 1922. Patient has had no trouble for over two months. Apparently cured. She has gained 10 pounds in weight and says she feels "fine."

**Summary and Conclusions.** 1. Hereditary hemorrhagic telangiectasia is characterized by the formation of localized dilatations of capillaries occurring, for the most part, during youth in the nasal mucosa. The telangiectases may appear elsewhere on the cutaneous mucosal and epithelial surfaces, though usually not until adult life is reached, and may be the seat of hemorrhages wherever they occur. The rupture of these vascular defects results from slight traumatism or from local congestion, vasomotor or irritative, and this explains the recurrent hemorrhages, particularly the epistaxis so prominent in this disease.

2. There is no demonstrable "hemorrhagic diathesis" in this disease.

3. Atavism is a factor which has not been sufficiently emphasized.

The literature discloses 212 afflicted individuals belonging to thirty families exhibiting the disease in classical form. There are seven instances of atavistic inheritance among these. The literature also contains reports of similar, though apparently non-hereditary cases which should be classed as atavistic examples of the disease.

4. The absence of characteristic family history does not preclude the diagnosis of this disease, which should be borne in mind in any case presenting obscure hemorrhagic phenomena. Especially suggestive is the analogy between this disease and certain cases of so-called essential hematuria, particularly the "hereditary hematuria" group.

5. Symptomatic cure can be accomplished for the majority of these patients by careful and, if necessary, repeated cauterization of the offending telangiectases.

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# AN EXPERIMENTAL STUDY OF THE MELTZER-LYON TEST, WITH COMMENT ON THE PHYSIOLOGY OF THE GALL-BLADDER AND SPHINCTER VATERI.\*

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NEW YORK.

**Introduction.** The historical footnote to the article in which Meltzer<sup>1</sup> discussed some phases of the physiology of the gall-bladder, particularly the law of contrary innervation, has given rise to considerable clinical and experimental work on the physiology and pathology of the biliary tract. In this footnote, he casually suggested the application of magnesium sulphate to the mucous membrane of the duodenum as a clinical method of therapy to dilate the sphincter, situated at the common duct, in cases of obstructive jaundice, whether of catarrhal origin or calculus blockage, thus utilizing the general principle of the magnesium radical as a depressor to smooth muscle and stimulant to the inhibitory fibers.

This suggestion visualized in the mind of Lyon,<sup>2, 3, 4, 5</sup> a definite physiological process with a definite train of events, which he utilized in the diagnosis and therapy of biliary diseases. The technic of the Lyon method is at this time too well-known to require any detailed résumé. Suffice it to mention that the introduction of about 50 cc of a saturated solution of magnesium sulphate into the duodenum by means of a duodenal tube, is followed, within a few minutes, by a deeply pigmented bile which Lyon has called the "B" bile. This "B" bile is usually of a rather viscid consistency and varies in quantity ordinarily between 30 and 60 cc. It is followed by a lighter, less viscid flow.

Lyon, noticing the similarity of the "B" bile to the contents of the gall-bladder as to color and viscosity, assumed that the "B" bile is gall-bladder bile. The validity of the Lyon method of therapy and diagnosis depends largely in attributing to the gall-bladder the origin of the dark "B" bile. It is this particular phase of the problem which has been of greatest interest. To prove the validity of these views a series of animal experiments were undertaken which differed from those of Crohn,<sup>6, 7</sup> in enabling us to carry on repeated observations for longer periods with the animal in the waking state.

The questions that present themselves for elucidation are as follows:

1. Does the deeply pigmented viscid bile originate in the gall-bladder?

\* The animal experiments herein recorded have been carried out in Prof. Bickel's Laboratory at the Pathological Institute of the Charité Hospital, Berlin, during the winter of 1921-1922. The surgical operations were performed by Prof. Bickel, for whose kind assistance the writer feels greatly indebted.

2. Does the gall-bladder contract and empty its contents in the sense of any other hollow viscus, like the urinary bladder?
3. Can the gall-bladder contract at all?
4. What is the function of the gall-bladder?
5. Is Oddi's muscle a sphincter in the true sense of the word?
6. What relation, if any, does it bear to the gall-bladder?
7. Does magnesium sulphate, or any other chemical substance, produce a dilatation of the sphincter and simultaneously cause the contents of the gall-bladder to empty its contents, thus bringing into play Meltzer's law of contrary innervation?

The solution of the physiological problems that presented themselves depended on the ability to obtain gall-bladder contents in dogs with the animal in a normal waking state. Crohn conducted a series of observations on narcotized dogs, in which he introduced methylene blue into the gall-bladder and studied the effect of various mechanical and chemical effects upon Oddi's sphincter and their bearing on the gall-bladder. Later, Bassler, Lockett and Lutz<sup>8</sup> observed the behavior of the gall-bladder during the course of laparotomies, the surgeon holding the gall-bladder between his fingers, while magnesium sulphate was applied through a previously introduced duodenal tube. The objections, however, that presented themselves in both instances were that conclusions were drawn with the subjects under deep narcosis. The blockage of the reflexes could have been responsible for the lack of the stimulus to the gall-bladder when the ampulla of Vater was stimulated chemically by the application of the magnesium sulphate or other substances.

It occurred to me that if such observations could be carried out with the animal in a normal state the conclusions thus drawn would be beyond criticism as to interference with the reflex arc. I therefore decided to establish a duodenal fistula and at the same time to introduce a foreign substance like a carmine emulsion into the gall-bladder, and when the animal recovered from the operation to inject through the duodenal cannula various chemicals and study their effects upon (a) the character of bile secreted; (b) character of gall-bladder contents; (c) the character of the bile during the digestive period and during the period of rest; (d) the interchange of hepatic bile with the gall-bladder contents, and (e) duration of gall-bladder stasis.

**Animal Experimentation.** The operation was performed as follows: Under ether anesthesia the gall-bladder was exposed. The fundus was then grasped by a clamp and brought to the opening of the wound. The needle of a record syringe was then introduced into the gall-bladder and about 5 cc of its contents withdrawn. A carmine suspension made up to about the same consistency as the gall-bladder bile was then injected into the gall-bladder through the same needle, the quantity injected being the same

as that withdrawn. A single stitch was then introduced at the point of the puncture and the gall-bladder allowed to drop to its normal position. The second step of the operation consisted in making a duodenostomy in the second portion of the duodenum, opposite the ampulla of Vater. A metal cannula was then introduced into the duodenal opening and held in place by a double row of stitches. This cannula was then brought through the abdominal wall by a puncture with a trocar and the wound was then closed. A small cork was introduced into the opening of the cannula so that there would be no constant leakage of the duodenal contents. The animal was then permitted to recover and for several days no observations were made.

The observations were conducted as follows: The animal, with a fasting stomach, was placed upon an elevated stand, the cork removed from the cannula and the duodenal contents allowed to flow into a glass container intermittently for several minutes at a time. It invariably contained bile of a golden-yellow appearance. Microscopical examination of the centrifuged specimen of this bile did not reveal at any time the presence of carmine granules. After a number of these observations, 20 cc of a saturated solution of magnesium sulphate was injected through a soft-rubber catheter inserted into the duodenum through the metal cannula with the point directed upward. The catheter was then withdrawn and the cork promptly replaced. After an interval of two minutes the duodenum was again allowed to drain. Such observations were repeated at two-minute intervals and carried on as long as a half hour and longer. The injections were then again repeated and the duodenal contents collected and examined.

At no time was there observed the appearance of carmine macroscopically. Occasionally a few carmine granules could be found microscopically after feeding the dog. Observations were conducted daily, not only was magnesium sulphate used for intraduodenal injections, but also weak solutions of HCl and peptones. Later on we also introduced magnesium sulphate solution into the stomach of the dog by means of a stomach tube, using about the same concentration. If the duodenal stopper was removed the pylorus became patent and most of the magnesium sulphate could be made to flow out of the cannula very rapidly, almost as fast as it was introduced into the stomach. At no time did it contain any carmine. The dog at all times was in excellent physical condition with the exception of the first day or two, and later did not seem to mind the injection of the various chemicals. After about four weeks' study on the first dog, a second dog was operated upon in a manner similar to the first, but withdrawing the entire contents of the gall-bladder and refilling it with a carmine suspension (10 cc) so that the gall-bladder became moderately distended. After three days the second dog was subjected to observations similar

to those made on the first and carried on for ten days. During the fifth week a third dog underwent a similar operation, the entire gall-bladder contents being removed and substituted by carmine emulsion, this filling the gall-bladder completely. Observations similar to those described were carried out for one week. At the end of this period all of the three dogs were killed by the injection of chloroform into the heart. Death was instantaneous in each case. The periods of observations were six weeks for the first, two weeks for the second, and ten days for the third dog.

The autopsy in each case revealed no inflammatory reactions around the gall-bladder as a result of the operation. There were no adhesions present around the cystic duct that would interfere with the outflow of the contents. The gall-bladder was removed intact and when held by the fundus the contents poured out freely. The gall-bladders were found normally filled. The contents in dogs Nos. 2 and 3 were made up of practically the entire carmine injected at the time of the operation; only a small amount of bile was found in the neck of the gall-bladder. Dog No. 1, in whom less than one-half of the amount was injected, still contained a small residue of the carmine, about  $\frac{1}{2}$  cc, showing that within six weeks there was no complete evacuation.

**Literature and Discussion.** The teachings transmitted through the older text-books in physiology attribute to the gall-bladder the function of a reservoir for the storage of the bile which comes down from the liver through the hepatic ducts in the fasting state and, during the active period of digestion, is discharged into the intestine. Stress is laid upon the concentration of the digestive ingredients of the bile and that with each stage of the digestion a concentrated bile is promptly supplied. More recent views hold that the act of emptying of the gall-bladder is produced by the reflex of the acid chyme entering the duodenum which causes relaxation of the sphincter at the ampulla of Vater, and through a reflex mechanism causes the gall-bladder to empty. Mann<sup>a</sup> in his discussion of the function of the gall-bladder subdivided it into three heads: (1) As a reservoir for storage of bile; (2) as a secretory organ; and (3) as a regulator to the flow of bile.

**RESERVOIR.** The implausibility of the gall-bladder functioning as a storehouse becomes apparent when we consider that the total secretion of bile for twenty-four hours in a normal man may rise to 1200 to 1500 cc and the capacity of the gall-bladder is only 30 cc, one-fiftieth capacity of the total volume secreted. In common duct obstruction due to calculi one never notices distension of the gall-bladder. Similarly, in the above mentioned experiments, a clear golden-yellow bile was invariably present in the fasting state. Through familiarity with the duodenal intubation we have come to learn that the bile flow is continuous even in the fasting state and that a steady non-intermittent flow can be noticed at all times.

CONTRACTION OF THE GALL-BLADDER. Through the valuable experiments of Bainbridge and Dale,<sup>10</sup> wherein they study the motor phenomena and the innervation of the gall-bladder by means of a rubber balloon introduced into the fundus of the gall-bladder, and connected with a manometer which registered the variation and tone, we learn that the gall-bladder is capable of undergoing very faint rhythmical contractions and slight changes in tone. In their studies on the innervation of the gall-bladder they were able to demonstrate that stimulation of the splanchnics, especially of the right, causes relaxation in the tone of the gall-bladder, especially in the region close about the neck. Bainbridge and Dale noted that the marked increase in tone reported by Doyon<sup>11</sup> was dependent upon extraneous causes, especially upon the changes in the liver volume. The enlargement of the liver which is observed as a result of sympathetic stimulation caused by the intravenous injection of adrenalin simulated the gall-bladder contraction. The changes in the liver volume are merely dependent upon the rise in blood-pressure, the contrast being more marked when the animal is bled, thus producing a very low blood-pressure prior to the adrenalin administration.

The parasympathetic effect which was obtained by a stimulation of the peripheral end of the vagus, especially of the left, was a slight augmentation in the tonal rhythm of the gall-bladder as noted with the manometer. No strong contraction similar to the muscular contractions of any hollow viscus was at any time noted. Neither is there any mention made of any observation on contrary innervation in the sense of Meltzer's assertion. These observations of Bainbridge and Dale made in 1905 are in accord with those of Lieb and McWhorter,<sup>12</sup> who, in 1915, studied the contractibility and tonicity of the isolated gall-bladder with the aid of drugs. They found that stimulation of the parasympathetic apparatus with pilocarpine and physostigmine produced increase in tone while atropine and adrenalin caused relaxation.

One therefore finds from the painstaking research of Bainbridge and Dale and Lieb and McWhorter that the gall-bladder is incapable of muscular contraction analogous to any other hollow viscus and that it is capable of only very slight changes in tonal rhythm which would be insufficient *per se* in causing the slightest evacuation of any of its contents. Our own experiments indicate the slow admixture of bile with the foreign substance and that foreign substances may be retained for weeks in the gall-bladder though the animal be kept in a normal state and properly fed.

SPHINCTER. While it is true that a sphincter at the ampulla of Vater exists and that it is capable of a slight tone, yet no one has been able to establish, in spite of the number of experiments carried out, any relation between this sphincter and the gall-bladder. Judd and Mann<sup>13</sup> report that the sphincter can withstand a pressure vary-

ing from 100 to 645 mm. of water and that the normal intraductal pressure, that is the secretory pressure of the liver, can withstand 230 mm. water and that it rises in cholecystectomized dogs to 360, in which cases the common ducts increase somewhat in diameter and muscular thickness.

One cannot speak of the sphincter as bearing a direct relation to the gall-bladder when we consider its anatomical situation. It is located several inches away from the neck of the gall-bladder.

One must consider the sphincter as an organ bearing direct relation to the common duct and to the intraductal pressure, regulating the opening into the intestines according to the rate of flow as it comes down from the liver, dilating somewhat to accommodate its rapid flow, which takes place in the digestive period or contracting when the flow disappears. The contraction of the sphincter is an important function, perhaps more important than the dilatation, and may be regarded as a protective measure to inhibit the regurgitation of the intestinal contents, food, digestive enzymes, and bile back into the biliary radicals and pancreatic duct. That the papilla of Vater is capable of contraction and that the contraction is an active process can be easily demonstrated by physical, mechanical or electrical stimulation of the papilla. The slightest faradization or passing the finger gently over it will cause a visible contraction and a raising of the papilla.

In our experiments where the papilla of Vater was daily bathed with magnesium sulphate and other chemicals for a period of weeks, we could not produce any reflex effect upon the evacuation of the gall-bladder contents. Neither did we see the discharge of its contents to any appreciable degree during the digestive period.

These may therefore be regarded as conclusive evidence as to (1) the absence of relation between the sphincter papilla and the gall-bladder, (2) the absence of reflex mechanism or contrary innervation between the sphincter papilla and the gall-bladder, whether (a) during the digestive period or (b) induced chemically by magnesium sulphate, etc.

Many clinical data have recently been accumulated, particularly by Dunn<sup>14</sup> and Dunn and Connell,<sup>15</sup> where the typical ABC sequences were obtained in cases with cholecystectomized individuals, impacted cystic ducts, and in a case of hepato-duodenostomy, where the gall-bladder and the common duct and all the large biliary radicals were absent, including even the sphincter papilla where a new anastomosis was made between the remnant of the hepatic duct and the duodenum. Similar changes in the physical characteristics of the bile were obtained by these observers when the magnesium sulphate was applied to distant parts of the intestine, in one instance as far as 32 cm. into the jejunum, and in others through application into the rectum and colon. These data further tend to invalidate the relation between (1) the sphincter



papilla and the gall-bladder, and (2) the application of Meltzer's law of contrary innervation to these organs. One must look elsewhere for the cause of the changes of the physical characteristics of the bile, and therefore the utilization of Lyon's test for diagnosis and therapy of biliary pathology becomes untenable.

**Conclusions.** 1. The function of the gall-bladder may be regarded merely as a slight overflow receptacle in the nature of a diverticulum of the common duct, devoid of contractile powers, which is merely able to receive small quantities of bile whenever the intraductal pressure rises higher than usual, the emptying of the gall-bladder being purely a passive act dependent upon mechanical factors. It is obvious that it never empties itself completely in the manner of any other contractile hollow viscus, but that occasionally small quantities may escape.

The retention of the carmine suspension in toto for about a week without any admixture of bile with the exception of a small quantity at the neck, and the presence of some carmine in the fundus of the bladder after six weeks when only one-half of the contents of the gall-bladder were replaced by carmine, prove the slow filling and emptying, the slow interchange of bile between the ducts and the gall-bladder.

That the gall-bladder possesses no special function may be adduced: (1) From the above experiments and also from Crohn's, whose results as regards retention of foreign substances introduced into the gall-bladder for long periods at a time were analogous; and (2) from the anatomical fact that certain species of animals like the horse, elephant and others have no gall-bladder and that it may be congenitally absent in man; and (3) that no untoward results or any pathological alteration were ever noted in the vast number of cholecystectomized individuals.

2. The sphincter Vateri bears no relation to the gall-bladder, either anatomically or physiologically. It does not form part of the gall-bladder structure. It is situated several inches from the gall-bladder. The experiments carried on by the writer failed to prove through stimulation of the sphincter any effect upon the gall-bladder contraction or evacuation of its contents. The experiments were conducted with the animal in the waking state and numerous observations were carried on daily, in one dog for a period of six weeks.

Clinical observations of Dunn, where the ABC bile sequences were obtained in cholecystectomized individuals and cystic duct blockage, and in the absence of the common duct and all bile radicals where a hepatoduodenostomy existed, further tend to disprove the selective action of magnesium sulphate upon the sphincter papilla and through it any contrary innervation causing contraction and evacuation of the gall-bladder.

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## REVIEWS.

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COLLECTED PAPERS FROM THE WASHINGTON UNIVERSITY SCHOOL OF MEDICINE. VOL. I, 1921. Pp. 1079; 347 illustrations. St. Louis: C. V. Mosby Company, 1923.

EXCELLENT as are the individual articles contained in this book, interesting as they may have been when they appeared in current literature, there seems to be little excuse for the gathering of them together in book form. Each article is available in the journal of its original publication and it would be referred to in that place by anyone desiring to read it. One can scarcely picture any physician purchasing the present volume, and indeed it will be of little value even to a medical library. The object of such a publication as is stated in the preface is to present primarily to the alumni of the institution the most recent contributions from that institution to medical research and experience. This object is certainly achieved and the contents of the book should make the alumni proud of the institution. P.

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TUBERCULOSIS IN INFANCY AND CHILDHOOD. By J. CLAXTON GITTINGS, M.D., Professor of Pediatrics in the Graduate School of Medicine, University of Pennsylvania; FRANK CROZIER KNOWLES, M.D., Professor of Dermatology in the Jefferson Medical College; and ASTLEY P. C. ASHHURST, M.D., Associate Professor in Surgery, School of Medicine University of Pennsylvania. Pp. 273; 23 illustrations. Philadelphia: J. B. Lippincott Company, 1922.

THIS book is composed of a series of lectures given at the Children's Hospital under the auspices of the Philadelphia Pediatric Society. It is destined to give to the general practitioner in a short comprehensive way all the essential elements necessary in recognizing and treating tuberculosis in all its phases in early life. The subject matter is clear and concise, beginning with a general chapter in which are considered the various subjects as: Types of tubercle bacilli, and their relative importance, childhood infection and immunity, modes of infection and so on. Other chapters are

devoted to the importance of a careful history, pointing out salient focal and constitutional symptoms combined with the physical examination. The value of various tuberculin tests is given. The various forms of tuberculosis found in early life are dealt with in full, including a separate chapter upon tuberculosis of the skin and another upon tuberculosis of bones and joints. The chapter upon miliary and generalized tuberculosis and meningitis is especially full and comprehensive, as well as the chapter upon the treatment of the tuberculous child. The book is well written and well deserving of a prominent place in the contributions upon tuberculosis. It is of special value to the general practitioners for whom the book was designed. K.

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DUFF HOUSE PAPERS. VOL. I. Edited by EDMUND I. SPRIGGS, M.D., F.R.C.P. Pp. 387; 197 illustrations. London: Oxford Medical Publications, 1923.

THE publishing in book form of scientific articles which have already appeared in current literature may be desirable from the point of view of the laboratory or institution from which they originated, but can be of little interest or value to the profession at large or even to medical libraries. The collection in book form serves to demonstrate the activities of the institution and can be employed for distribution to benefactors but the gathering together of heterogeneous articles in a book can serve no useful scientific purpose. In the volume under discussion there are articles on the gastro-intestinal tract, diabetes, pancreatic insufficiency, sprue, etc. P.

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PRINCIPLES AND PRACTICE OF X-RAY TECHNIC FOR DIAGNOSIS. By JOHN A. METZGER, M.D. Roentgenologist to the School for Graduates of Medicine, Medical Department, University of California, Southern Division, Los Angeles. Pp. 144; 61 illustrations. St. Louis: C. V. Mosby Company, 1922.

In this manual the author has concisely presented some of the fundamentals of roentgen-ray technic. The photographic reproductions are unusually good. These with the aid of the text gives one a very good idea as to the positions in which various parts of the body are examined. Most of the positions are more or less standardized, but in others, the author has presented his own technic, and these may vary somewhat with different workers. In addition to the preparation of the patient, the author gives his table of exposure for each examination, which will be of considerable help to one unfamiliar with this type of work. P.

CEREBROSPINAL FLUID IN HEALTH AND IN DISEASE. By A. LEVINSON, B.S., M.D., Associate in Pediatrics, Northwestern University Medical School. Second edition. Pp. 267; 69 illustrations, including 5 colored plates. St. Louis: C. V. Mosby Company, 1923.

IN the four years since his first edition the author has brought his monograph up to date. Thirty-six pages and thirteen illustrations have been added. Indications and contraindications for lumbar puncture are tabulated and the method of cistern puncture is described in brief. Recent advances in chemistry of spinal fluid are incorporated in the new chapter of physico-chemical properties. The cytology is more accurately described and recent studies of diseases are added. Very little new has been added on treatment and no mention is made of the therapeutic value of spinal drainage. The bibliography has also been brought up to date. This monograph is a valuable one to the laboratory worker, student and clinician alike and enables one to obtain all the essential information of the subject. B.

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GRUNDRISS DER HYDROTHERAPIE. By DR. WALTER KREBS, Chefarzt des Landesbades der Rheinprovinz in Aachen. Second edition. Pp. 149; 10 illustrations. Bonn: A. Marcus & E. Weber, 1923.

A SHORT treatise on: (1) The effect of hydrotherapy on various physiological functions (15 pages); (2) the technic of various hydrotherapeutic methods (47 pages); (3) its application in various diseases (83 pages). K.

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PRACTICAL BACTERIOLOGY, BLOOD WORK AND ANIMAL PARASITOLOGY. By E. R. STITT, A.B., Ph.G., Sc.D., LL.D., Rear Admiral, Medical Corps, and Surgeon-General, U. S. N., etc. Seventh edition. Pp. 15 and 766; 203 illustrations. Philadelphia: P. Blakiston's Son & Co., 1923.

OF today's various laboratory manuals none could be less easily dispensed with than this one. It continues to astonish the grateful user with the amount and variety of accurate information condensed in small space and presented in easily available manner. Since its last review in this Journal (1918, 155, 133), the volume has been increased by over 200 pages, 132 of which were added in this seventh edition. This has permitted the addition of "a summary of the subject of nutrition," a fuller treatment of methods

of immunity, the protozoa and mosquitoes, a large number of new tables, description of flocculation tests for syphilis, etc. By a typographic error in the table of contents, the pagination of Chapters XXXVI and XXXVII has not been altered from the sixth edition.

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**TONSILLECTOMY BY MEANS OF THE ALVEOLAR EMINENCE OF THE MANDIBLE AND A GUILLOTINE, WITH A REVIEW OF THE COLLATERAL ISSUES.** By GREENFIELD SLUDER, M.D., F.A.C.S., Clinical Professor and Director of the Department of Rhinology, Laryngology and Otology, Washington University School of Medicine. Pp. 176; 90 illustrations. St. Louis: C. V. Mosby Co., 1923.

IT is with a great deal of enthusiasm that we welcome the writer's publication on tonsillectomy. "The Sluder operation" for the removal of tonsils has been tried and tested throughout the world, until its importance in the field of laryngology has been firmly established. It has become one of the modern standard operations and it is right and proper that its author should see to it that the proper technic be plainly set before the laryngological world. In doing this, the writer has gone carefully into the whole tonsillar question, though the surgical part of the monograph is limited to the technic of the Sluder operation and the removal of adenoids by direct visions, the latter subject being written by Dr. I. D. Kelly. A very important part of the book is the chapter on physiology and general pathology of the tonsil, written by Arthur W. Proetz. Although we cannot agree with some of the views expressed, this review of the tonsil question is really one of the most carefully written articles on the subject. One of the most impressive features of the book is the apparent study that the author has made of the literature on the subject, and the room given to the opinion of other authorities. There is a fairly complete appended bibliography. The work is profusely illustrated, the large majority being original microphotographs and drawings. We recommend this book to the beginner and to the skilled specialist; the general practitioner will find much of interest in its pages—the mature utterance of one of the world's great specialists.

W.

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**TUBERCLE BACILLUS INFECTION AND TUBERCULOSIS IN MAN AND ANIMALS.** By ALBERT CALMETTE, Associate Director, Pasteur Institute, Paris. English translation by W. B. SOPER, Saranac Lake, and G. H. SMITH, School of Medicine, Yale University. Second edition. Pp. 714; 56 illustrations. Baltimore: Williams & Wilkins Company, 1923.

THIS is a splendid translation of a very worthy book. The author has built a monument on the subject of tuberculosis by

virtue of his intimate knowledge of the subject. It includes not only the researches of the author and his pupils, but in addition a summary of our knowledge of tuberculosis. Beginning with its history, he traces its development, and takes up every conceivable point, with the result that a complete book has been attained. The physician, the veterinarian, the laboratory investigator and the preventive worker will find the book equally important and equally suggestive of ideas. The illustrations, particularly the full color plates, are a strong asset to the text. J.

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**INFECTION AND RESISTANCE.** By HANS ZINSSER, M.D., Professor of Bacteriology and Immunity, Harvard Medical School. Third edition. Pp. 666; numerous illustrations. New York: Macmillan Company, 1923.

ALTHOUGH Prof. Young's chapter on Colloids has been omitted from this edition, it is eighty-one pages longer than the second, which appeared in 1919. This is brought about both by small additions throughout the book and by the revision and increase of the chapters on anaphylaxis and practical therapeutic methods and theories, with new chapters on iso-antibodies and the nature of antibodies. In spite of a certain obscurity of style, which makes a complex subject doubly difficult to read, this new edition should be welcomed by student and teacher alike. K.

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**THE ANTIQUITY OF DISEASE.** By ROY L. MOODY, Associate Professor of Anatomy in the University of Illinois. Pp. 148; 36 illustrations. Chicago: University of Chicago Press, 1923.

ONE of the few complaints to be made about this latest contribution to the University of Chicago Science Series is that it is much too short. Although the author is a well-known authority on the subject (he is also the editor of Ruffer's *Studies in the Palæopathology*) and has selected wisely, it has not been possible, and probably not even attempted, to give a clear picture of the comparative pathology of the ages within such small scope. The glimpses afforded into the beginnings of disease, fossil pathology and primitive human pathology and surgery, should, however, furnish ample stimulus to the reader to go further into this fascinating field.

The pictures of the oldest known bone tumor (a hemangioma of a dinosaur) and oldest known fracture (a transverse break of the radius of a Permian reptile) inevitably lead one on to neolithic

evidences of fracture and bone tuberculosis, prehistoric trephines, early Egyptian spondylitis, schistosomiasis, splenomegaly, described in the final chapters. It is interesting to know that although bacteria are among the oldest inhabitants of the earth, and may even have initiated life on this earth by being carried from distant planets on meteorites, they were not for ages connected with disease. "Disease was not present in the earliest times of the earth's history" and "it is only after the great Coal Period that infected wounds are found." Surely more attention to such studies and to the cognate subject of the history of medicine will not only afford pleasant reading to the modern medical man, but will develop a perspective capable of rendering material aid in defeating the various cults that now hamper medical practice.

K.

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OUTLINES OF MEDICAL ZOÖLOGY. By R. W. HEGNER, W. W. CORT and F. M. ROOT, of the Department of Medical Zoölogy, School of Hygiene and Public Health, the Johns Hopkins University. Pp. 175; 21 plates. New York: Macmillan Company, 1923.

THIS small hand-book is intended for the use of public health officers, students and physicians, especially those practising in tropical or semitropical countries. For greater simplicity, many of the lesser known species of parasites have been omitted. Its three parts consider: (1) Protozoa parasitic in man; (2) worms parasitic in man; (3) arthropods of medical importance. The material is well presented and should prove useful to workers in this field.

K.

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BACTERIOLOGY (A STUDY OF MICROÖRGANISMS AND THEIR RELATION TO HUMAN WELFARE). By H. W. CONN, PH.D., formerly Professor of Biology at Wesleyan University and Bacteriologist of the State Board of Health of Connecticut; and HAROLD J. CONN, PH.D., Soil Bacteriologist at the New York Agricultural Experiment Station. Pp. 441; 48 illustrations. Baltimore: Williams & Wilkins Company, 1923.

THE authors present the scope of the book in a descriptive subtitle as "Discussing the History of Bacteriology, the Nature of Microörganisms and Their Significance in Connection with Pathology, Hygiene, Agriculture and the Industries." The history of bacteriology is presented in a most interesting manner and should tend to give the beginner in bacteriology the proper perspective. The various activities of microörganisms, their relations to the



fertility of the soil to the various industries and to Public Health are discussed in a style which will hold the reader's attention and with detail enough to broaden the viewpoint and to win the student's profound respect for this young science. A section on Pathogenic Microorganisms records briefly the facts necessary for a first acquaintance with this subject. The introduction of Plant Bacteriology and its relation to certain plant diseases rounds out the work. The book is well adapted for collegiate courses in general bacteriology. S.

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A MANUAL OF ARTIFICIAL RESPIRATION. By CAPT. G. R. G. FISHER, with the American Red Cross overseas during the World War; Director, Bureau of First Aid, Northern Division, A. R. C.; Director of Accident Prevention and Instructor in First Aid to Industries and Civic Organizations of the City of Omaha, Nebraska. Pp. 80; 22 illustrations. Boston: The Stratford Company, 1923.

THIS small brochure will give to the teachers of first aid a manual which can be used for a text-book in teaching artificial respiration. It is well illustrated and the subject matter is accurately presented. M.

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CHRONIC FATIGUE INTOXICATION. By EDWARD H. OCHSNER, B.S., M.D., F.A.C.S., Attending Surgeon, Augustana Hospital; President-elect, Illinois State Medical Society. Pp. 143. New York: G. E. Stechert & Co., 1923.

THE author takes for his theme the chronic fatigue intoxication, a chronic systemic disorder, which is produced as a result of accumulation in the tissues of excessive amounts of fatigue material. In the monograph he proceeds to show how the present-day individual, under the stress and strain of modern life, may develop a large number of symptoms which manifest themselves in as many ways as such a pleomorphic disease as syphilis, and which will eventually lead to a large variety of chronic degenerative diseases. The appearance of a book such as this from the pen of a surgeon should not be considered as a reflection on the internist, but rather it should rebound to the honor of one who has the ability to appreciate and to recognize this heretofore inadequately described affliction. M.

# PROGRESS OF MEDICAL SCIENCE

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## SURGERY

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UNDER THE CHARGE OF

T. TURNER THOMAS, M.D.,

ASSOCIATE PROFESSOR OF APPLIED ANATOMY IN THE MEDICAL SCHOOL AND  
ASSOCIATE PROFESSOR OF SURGERY IN THE SCHOOL FOR GRADUATES  
IN MEDICINE IN THE UNIVERSITY OF PENNSYLVANIA; SUR-  
GEON TO THE PHILADELPHIA GENERAL AND  
NORTHEASTERN HOSPITALS.

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**Cause of Death in Intestinal Obstruction.**—BRINGLE (*Lancet*, 1923, 205, 63) says that cause of death in intestinal obstruction is still a subject for debate. Three theories have been advanced: infection; absorption of toxins from the obstructed intestines; and depletion of systemic circulation and cerebral anemia. Research work has shown that the principal factor in causing death in intestinal obstruction is a toxin which is developed chiefly in the duodenum, and although not absorbed from the normal intestine, is absorbed under the conditions which prevail in obstruction. The exact chemical composition of the toxin is still under dispute, but it is almost certainly of the nature of the toxic bodies derived from protein disintegration. The exact mode of production of the toxin is also undecided but probably the presence of pancreatic secretion, and in lesser degree the activities of bacteria are necessary for its production. Clinical observations and experience agree with these experimental findings.

**Radiography in the Examination of the Urinary Tract.**—SUTHERLAND (*Jour. Radiol.*, 1923, 4, 221) says that much interest has been expressed regarding the findings and technic in the roentgenological examination of the urinary tract. One thousand consecutive histories were studied, in which the urinary tract had been examined roentgenologically. In these cases, a total of 75 calculi were found by cystoscopic and surgical examination, 41 in the kidney, 24 in the ureter and 10 in the bladder. The section on roentgenology reported 37 of the 41 in the kidney, 14 of the 24 in the ureter and 6 of the 10 in the bladder. Thirty-one shadows diagnosed from roentgenograms in the kidney areas as calculi or suggestive of calculi were ruled out, or were not found at cystoscopic examination. Six of the 10 calculi found in the

ureters had been reported by the section as phleboliths. Phleboliths were reported in 376 patients. Shadows were often seen in the roentgenograms of areas embracing the urinary tract, which were not seen in subsequent re-rays of the same areas. Eliminating the rare passing of a stone, the conclusion must be that these shadows were cast by small concretions or particles of insoluble matter in the bowels. Several cases have been seen in which small warts on the skin have cast shadows, which were difficult to distinguish from calculi. Roentgenological evidence, therefore, cannot be accepted as final, but should be checked up by urological investigation and correlated with the clinical evidence.

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**Chronic Mastitis.**—KEYNES (*Brit. Jour. Surg.*, 1923, 11, 89) says that the breast is a secreting gland which shows periodical activity from birth to menopause. The normal non-lactating breast has no outlet through the nipple for the discharge of its secretions. Secretion must, therefore, be balanced normally by reabsorption. Chronic mastitis is manifested by dilatation of ducts and acini, accumulation in them of the products of epithelial activity, infiltration with lymphocytes, fibrosis and epithelial changes. Distribution of all these is very erratic. Chronic mastitis, more common in women, first appears in second decade, but is most often seen in the fifth. Chronic mastitis is not bacterial in origin, toxemic or traumatic. The cause of chronic mastitis is probably to be found in chemical irritation, due to stagnating secretions and epithelial debris. Chronic mastitis, though very often associated with carcinoma, has not been proved to be pre-cancerous.

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**A Case of Heart and Respiratory Failure in High Spinal Anesthesia (Saved through Heart Massage).**—PHILOPOWICZ (*Zentralbl. f. Chir.*, 1923, 24, 961), a lawyer, aged sixty-five years, showed signs of hematuria of five years standing, with marked myocarditis, arrhythmia, deep bronchitis, and emphysema. The left kidney was involved by an immovable mass, the size of a child's head. The urine showed macroscopical blood. Hypernephroma without evident metastasis was the diagnosis. General anesthesia was contraindicated, local anesthesia was not feasible in this individual case; spinal anesthesia with stovaine and strychnine alone remained. During the abdominal opening, the patient took one deep breath, and did not regain heart action and respiration after injection of the usual restoratives. The writer grasped the apex of the heart, and gave routine massage. After one minute, the heart began to beat slowly and faintly; gradually, respiration was restored, at first Cheyne-Stokes in type. With an experience of 2000 cases of spinal anesthesia, this was the author's first irregularity. The operation was completed and uneventful convalescence occurred.

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**End-results in Malignant Disease of the Testes.**—COLÉY (*Ann. Surg.* 1923, 78, 370) says that the number of permanent cures following surgical removal of the testicle for malignant disease is comparatively small, the proportion being not over 5 to 10 per cent. This number of cures, in his opinion, is not sufficiently increased by the radical operation of removal of the retroperitoneal glands by the abdominal route, to warrant the very considerable risk of such an operation. Long continued systemic treatment with the mixed toxins of erysipelas and

*Bacillus prodigiosus*, combined with thorough radiation of the abdomen and supraclavicular glands by radium or roentgen-rays offers a far better hope of permanent cure than any form of operative treatment alone. If one waits after operation until a recurrence has taken place, marked regression of these recurrent tumors and in some cases complete disappearance may be expected from the radium treatment. In the great majority of the cases the regression or disappearance will prove only temporary and death from extension of the disease will occur.

**Metastatic Hypernephroma.**—GIBSON and BLOODGOOD (*Surg., Gyn. and Obst.*, 1923, 37, 490) say that hypernephroma is a comparatively rare condition. Bone is a tissue of predilection for this tumor. The pathogeny of the hypernephroma is still *sub judice*. Metastasis to bone is chiefly *via* the blood stream. The bony metastasis is sometimes the only metastatic focus. Complete skeletal roentgenographical examination should be made in every suspected case. While mainly a lesion of later middle life, it is found in the young. The malignancy of the condition varies enormously. A solitary bone metastasis may be extirpated with good ultimate result. In the presence of cachexia or multiple bone metastases, palliative measures only are advisable.

**Quantitative Studies in Syphilis from a Clinical and Biological Point of View.**—FORDYCE, *et al.* (*Am. Jour. Syph.*, 1923, 7, 444) says that analyses of the blood for its arsenic content after intravenous injections of silver arsphenamine were made in 299 specimens obtained from 214 patients. It was found that 56.4 per cent of the arsenic injected-localizes outside the blood stream immediately after completion of the injection. Observations made at intervals of from five minutes to one day show that there is a gradual lowering of the arsenic equilibrium in the blood based on average values. Observations made after a period of one day show first a marked increase in arsenic content, and then a gradual diminution at later intervals based on average values.

**Chancre of Lip.**—PAROANGIAN and GOODMAN (*Am. Jour. Syph.*, 1923, 7, 563) cited a number of case histories showing the difficulty of diagnosis in chancre of the lip. As the authors see the problem, the physician first consulted has the ultimate fate of the case in hand. If syphilis is not suspected, and the cases cited seem to prove that it is not, the patient goes through the generalized period of syphilis, and all that pertains to it. The benign appearance of early lip chancre is certainly deceptive, or else the physician is loath to consider the possibility of such a diagnosis. In most instances, the picture of lip chancre as ordinarily illustrated in text-books seems a terrible lesion indeed, and one which could never be overlooked. Unfortunately, the lip chancre of syphilis does not always follow the text-book, and as the author's photographs show, many a harmless lesion harbors the spirochete of syphilis, and unless checked by the proper treatment, the course of syphilis runs on. The dark field and the Wassermann, but above all clinical acumen and experience are needed for the diagnosis and ultimate abatement of the process of syphilis in the patient with lip chancre.

## THERAPEUTICS

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UNDER THE CHARGE OF

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AND

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**The Administration of Insulin by Inunction.**—As a result of experiments on rabbits, TELFER (*Brit. Med. Jour.*, April, 1923, p. 715) concludes that insulin can be introduced into the blood stream by inunction. This method of administration necessitates the use of much larger quantities of the drug than those required to produce comparable effects by subcutaneous injection; however, the results suggest that in this method crude insulin extracts might be utilized. As the cost of isolating the drug in a pure and active state for the purposes of hypodermic medication is so great as to restrict seriously its application on a large scale, it is possible that more liberal use of cruder materials might with advantage be made by means of inunction.

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**Serological Factors of Natural Resistance in Animals on a Deficient Diet.**—SMITH and WASON (*Jour. Immunol.*, 1923, 8, 195) state that the sera from animals which had been maintained upon a rickets-producing diet show certain differences when compared with sera from normally fed animals. The outstanding feature is the marked difference in the bactericidal titers; values for the most active sera among the rachitic rats being well below the lowest values secured for the normal animals. The complement titrations show but little variation, and there appears to be little if any correlation between complementing activity and the bactericidal values of the serum. The phagocytic indices, while subject to considerable variation within each group, appear in general somewhat lower among the animals fed upon the deficient diet. It is of particular interest that these serological titrations upon the group of rats which had been upon a deficient diet failed entirely to show any consistent difference which could be correlated with the anatomical findings reported by Powers (*Johns Hopkins Hosp. Bull.*, 1922, 33, 125). Both groups, those which actually showed rickets and those which, because of radiation, failed to show rickets, were essentially alike in regard to the reactivity of their sera. It is not suggested that these changes may be fundamental or that they may be directly associated with the defective diet. It is indeed much more probable that they are indirect, being dependent upon a modified cellular activity induced by failure to provide a proper regimen. Observations quite similar to those have been made upon a large series of rats which have been put upon defective diets in various respects. In not all cases have the results been comparable to those here reported, but the general outcome of the experiments has been quite analogous to the findings in this particular series.

**Etiology of Dengue Fever.**—CHANDLER and RICE (*Am. Jour. Trop. Med.*, 1923, 3, 233) describe an epidemic of dengue of unprecedented proportions originating in Galveston in June, 1922, which spread over all of eastern and central Texas and into neighboring states. Between 500,000 and 600,000 cases were estimated to have occurred in Texas. The authors state that the organism of dengue, shown by previous workers to be a filtrable virus in the blood plasma, has been suspected of being a *Leptospira* on account of a supposed relationship of the disease to yellow fever. This relationship is probably overemphasized. Dark-field examination of blood smears, inoculations into guinea-pigs, mice and monkeys, and attempts to cultivate the organism in media used for *Leptospiræ*, all gave negative results. Negative findings, in blood, in inoculated animals (particularly guinea-pigs), and in cultures; the usual absence of liver and kidney involvements; the fact that the relationship of dengue to yellow fever has been overemphasized; and the viability of the virus in blood kept in an ice chest after removal from the host (according to Cleland, Bradley and MacDonald) led the authors to believe it improbable that the organism of dengue is a *Leptospira*. Previous experimental work and epidemiological evidence point to *Aedes ægypti* (*Stegomyia fasciata*) as the principal transmitter of dengue, this species being replaced principally by *Aedes* (*Stegomyia*) *scutellaris* in Formosa. *Culex quinquefasciatus* (*fatigans*) has been incriminated on very slender evidence. The Texas epidemic was accompanied by an unprecedented scourage of *Aedes ægypti*, and the epidemiological evidence points very strongly to the agency of this mosquito in transmission, and suggests that *Culex quinquefasciatus* played a very minor part, if involved at all. Transmission experiments carried out with *Aedes ægypti* were successful in 4 out of 6 cases; the mosquitoes succeeded in transmitting the disease in from twenty-four to ninety-six hours after feeding on patients in the second to fifth days of the disease. The incubation period in experimentally infected cases, both when bitten by infected mosquitoes and when inoculated with a patient's blood, varied from four days and two hours to six days and twelve hours.

**Indices of Nutrition.**—CLARK, SYDENSTRICKER and COLLINS (*Pub. Health Rep.*, 1923, 38, 1239) summarize an extensive and apparently carefully made study as follows:

1. For the purpose of comparing different indices of nutrition, a group of 506 children who had the following qualifications were selected from much larger numbers: (a) Native white of native parentage and native grandparents; (b) no physical defects; and (c) nutrition "good" or "excellent" as judged from clinical evidence.

These children were selected after careful physical examination as being in good health so far as the medical examiner (United States Public Health Service) could determine.

2. Three standards of weight were applied to them. It was found that according to the Wood standard (height-weight-age tables), 20 per cent of these children were more than 10 per cent underweight; according to Dreyer's standard (stem length and chest circumference tables), 13 per cent of the children were more than 10 per cent underweight; and according to Pirquet's "pelidisi" method, 17 per cent had pelidisi of 94 or less and were underweight according to this standard.

3. A cross tabulation was made to ascertain whether children underweight according to one standard were underweight according to other standards. Although the percentage of children who were underweight did not vary greatly when different standards were applied (13, 17, and 20 per cent), many individuals classed as underweight by one standard were classed as normal or, in a few cases, overweight, by one or both of the other standards. Out of 506 children, 210 were classed as underweight by one or more of the three standards used; of these 210 cases, all three standards agreed on 15 cases as being underweight.

These children were selected as the best specimens of health that could be found among school children. In spite of this fact, one-fifth of them were underweight according to the standard most frequently used in school health work in the United States.

**Physiological Effects of High Temperatures and Humidities With and Without Air Movement.**—SAYERS and HARRINGTON (*Pub. Health Rep.*, 1923, 38, 1616) made an experimental study of this subject which is summarized by the authors as follows:

A. Remaining at rest in saturated air at  $91\frac{1}{2}^{\circ}$  F. for one hour,

With no air movement caused—

1. An increase in body temperature;
2. A moderate increase in pulse-rate;
3. Profuse sweating;
4. After effects of dizziness and weakness.

With air movement caused—

1. Slight or no increase in body temperature;
2. Slight increase in pulse-rate;
3. Slight perspiration;
4. No after effects;
5. No ill effects at any time; but the noise of the fan was annoying.

B. Remaining at rest in saturated air at  $95^{\circ}$  F, for one hour,

With no air movement caused—

1. An increase in body temperature;
2. A marked increase in pulse-rate;
3. Very profuse sweating, clothing being saturated with perspiration and sweat in shoes of all subjects;
4. Dizziness on movement, and increase in depth and rate of respiration (puffing somewhat on slight movement); chilly sensations in some subjects.

With air movement (250 to 600 linear feet per minute) caused—

1. Slight or no rise in body temperature;
2. Slight or no rise in pulse-rate;
3. Profuse sweating, but not sufficient to wet all clothing;
4. No untoward symptoms in subjects other than profuse sweating.

C. Remaining at rest in saturated air at  $96^{\circ}$  F., still and moving, caused the subjects to experience symptoms practically the same as those felt in still or moving saturated air, respectively, at  $95^{\circ}$  F.

D. Remaining at rest in saturated air at  $98\frac{1}{2}^{\circ}$  F. for one hour,

With air movement caused—

1. An increase in body temperature;
2. An increase in pulse-rate (in one case to 183);
3. Very profuse sweating, clothing being saturated (sweat could be poured from shoes);
4. Dizziness on movement. All felt that little work could be done at this temperature and that the conditions were much worse than in moving saturated air at 95° F., but not as bad as moving saturated air at 100° F.

E. Remaining at rest in saturated air at 100° F.,

With no air movement caused—

1. A marked rise in body temperature, which reached 102.3° F.;
2. A marked rise in pulse-rate, varying in different subjects more 152 to more than 175;
3. Profuse sweating, the shoes being partly filled with perspiration;
4. Early appearance of dizziness, weakness, and persistence of symptoms for about one hour after test. The test was very trying.

With air movement (200 to 800 linear feet per minute) caused—  
All the above symptoms, and no subject remained a full hour.

The untoward effects upon man of almost saturated air with temperature above 90° F. and below 98° F. are much less when the air is moving than when it is still. Further, the output or work that can be done is greater when the air is moving than when it is still, with the above temperature and humidity.

No beneficial effects were found by moving saturated air at 98.6° or 100° F., even at high velocities; and there was apparently some disadvantage.

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**A Possible Explanation of the Absence of Bubonic Plague in Cold Countries.**—ROBERTSON (*Pub. Health Rep.*, 1923, 38, 1519) concludes his study as follows:

"The more obvious conclusions to be drawn from this discussion and these tables are as follows: (1) Bubonic plague is essentially a disease of hot climates, and, having been introduced into tropical countries, it tends to persist indefinitely; (2) outside of the immediate Tropics, this disease is rather definitely limited in the extent to which it will spread; (3) in countries with a mean midwinter temperature of 45° F. or below, bubonic plague is occasional, accidental, and distinctly self-limited, and it seems possible for it to occur in the colder regions only for short periods under unusual conditions.

"This study appears to me to sustain the deduction that the seasonal prevalence of fleas regulates the spread of bubonic plague; otherwise it becomes necessary to find at least some equally reasonable explanation for the absence of bubonic plague in cold countries.

"Any estimate of the practical results that would ensue from a determination of the correctness of the theory advanced in this article and the conclusions drawn therefrom must await confirmation by an actual and comparative flea survey of any given locality."



## PEDIATRICS

UNDER THE CHARGE OF

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**Cicatricial Stenosis of the Esophagus Caused by Commercial Lye Preparations.**—CLERF (*Jour. Am. Med. Assn.*, 1923, 80, 1600) reports a number of cases in which, as in practically all cases of esophageal stenosis resulting from lye preparations, an analysis of the circumstances attending the ingestion of the alkali revealed several points of interest. The swallowing was practically always accidental, the lye, in powder or solution, having been left in reach of the child, or put on the kitchen shelf with other containers and mistaken for one of these. Sometimes it was a residue adhering to a cup which had been used for measuring the lye. This apparent carelessness was due to a lack of knowledge of the highly poisonous nature of all lye preparations. Since lye may be purchased anywhere, and since the labels on the containers either have no poison or warning notice, or if present is inconspicuous, it is seen that education as to the poisonous nature of lye is only by bitter experience. It seems difficult to understand why necessary legislation has not been provided to prevent these sad occurrences by adequate notice on the label. Similar precautions as are used for other poisons could be taken with lye to warn the public of the highly poisonous nature of these substances. Then it would be placed beyond the reach of children.

**Clinical Study of Thirty Cases of Muscular Dystrophy.**—FUNSTEN (*Jour. Bone and Joint Surg.*, 1923, 5, 190) analyzed 30 cases, 4 of which were of the juvenile form, coming on at the ages of twelve, fifteen, eighteen and twenty-one years, and usually starting as the upper girdle type. The other 26 were of the infantile form, and more frequently started as the girdle type, the weakness being noted in the lower limbs, with difficulty in getting up from the floor, and in going upstairs. Stumbling, lordosis, waddling gait and the loss of reflexes were the characteristic symptoms. Twenty-four of these were of the infantile type, either the hypertrophic or the atrophic forms. There were 2 cases of the fascio-scapulo-humeral type. Seven cases were beyond the walking stage and had various contractures. Twelve cases were treated for from four weeks to three months with various glandular extracts without any appreciable effect. Seven cases were treated with calcium lactate and 11 with massage and exercises with or without glandular treatment. It is felt that the calcium lactate was of some benefit. Wassermann tests were made in 14 cases and were negative. The microscopical blood picture was normal in the 6 cases examined. The reflexes were either absent or greatly diminished in all cases, with the exception of the cremasteric and abdominal reflexes, which as a rule were present. Microscopical examination of the muscle made in 4 cases showed the fibers to be pale, with diffuse areas of granular degeneration and vacuolization. There were also areas of

infiltration between the muscle fibers. The striations were present, except in a few places where complete degeneration had taken place. Of this series of 30 cases 23 patients are known to be living, 3 are dead from intercurrent diseases, and 4 have not been recently heard from. In none of these cases was there any tangible connection between the onset of the disease and acute infectious diseases. In no case was the onset acute.

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**Agglutination Test for the Presence of Bacillus Diphtheria in Field or Mixed Cultures.**—FITZGERALD and DOYLE (*Jour. Am. Med. Assn.*, 1923, 80, 1675) found in 52 cultures, which on smear examination were reported positive, 47 gave a positive agglutination with one or both types of serums in dilutions up to 1 : 640. The remaining 5 cultures were not agglutinated with either serum. This was probably due to the fact that they were representatives of other agglutination types of *B. diphtheriæ*. Of the cultures reported negative on smear examination, 52 in all, 47 also gave negative agglutinations. The remaining 5 cultures, reported negative from smear examination, gave positive agglutinations. These discordant results are of considerable interest. The first culture was sent to the laboratory for examination for release from quarantine, and was taken from a convalescent carrier, from whom 23 cultures in all had been taken. Agglutinations were positive in dilutions of 1 : 640 with both type serums. The second positive agglutination test obtained when a negative smear was reported was with a culture for first diagnosis. This culture was taken from a student who had had a mild sore throat for several days, and had received local treatment. A second culture taken from this man some days later was negative both by smear and by agglutination tests. A third positive agglutination with a culture on which a negative smear report was given was a culture for first diagnosis. This was from a child four years of age who had had a sore throat for several days. A physician found a spot on the tonsil which he diagnosed as diphtheria. Another physician said that the disease was not diphtheria, but took a culture. This was negative by smear but positive by agglutination tests. The spot was easily removed and did not bleed and recovery took place without the use of antitoxin. Positive agglutination tests were obtained in two other instances in which the negative reports on smears were made. These cultures were taken to test for release and were from convalescent carriers. There seems to be a certain amount of presumptive evidence in these 5 cases that the agglutination reactions which were positive although smears were negative, may have more correctly reflected the true condition. Spontaneous agglutinations may occur in dilutions of 1:10 with field cultures agglutinated with specific diphtheria agglutination serums. This has not been encountered in higher dilutions. Inhibition of agglutination, the so-called prezone phenomenon was not observed in the agglutination of field cultures. This has been noted, however, in agglutinations of pure cultures of *B. diphtheriæ* by monotypical serums. Field cultures taken twenty-four hours previously have been employed as antigens, but the growth as a rule is less luxuriant, and the preparation of satisfactory emulsions for antigens is difficult. Rapid agglutination tests by the centrifugalization of mixtures for agglutinating serums and emulsions of field cultures

have corresponded with those obtained by the technic described in detail by the authors. When the rapid method is used, results can be read about thirty minutes after the mixtures of antigen and agglutination serums are made and then centrifugalized for five minutes. This means that the entire procedure may with this method become completed within twenty-four hours after the original field culture has been taken. Cultures have been made from 4 definite clinical cases of diphtheria and the results of smear examinations, intracutaneous virulence tests and specific serum agglutination have been correlated. In these few instances there was complete correspondence in the results obtained.

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**Bacterial Endocarditis in Congenital Heart Disease.**—CLARKE (*Jour. Am. Med. Assn.*, 1923, 81, 371) says that there can be little doubt that the association of endocarditis and congenital heart disease is more than a coincidence. Their rather frequent association, in view of the rarity of the primary condition, lends additional weight to the statement that endocardial infections occur in hearts on previously damaged or altered surfaces. The case reported gave a history of rheumatic fever, and although no evidence of rheumatic heart disease was found post mortem, this may have contributed to his susceptibility to bacterial endocarditis. This condition is manifested in many ways, and is frequently diagnosed as typhoid fever, meningitis or malaria, and it resembles the latter condition so closely that at one time the French thought that malaria might be the cause of the condition. The predisposition of patients with congenital and acquired heart disease to bacterial endocarditis is a stumbling-block in the recognition of the disease. The knowledge of the presence of a cardiac condition is likely to lead the mind of the medical attendant away from the proper diagnosis of the fever and associated signs of infection. It should be emphasized that a fever of irregular type, of which the cause is not obvious, in a patient who has heart disease, should lead to a suspicion on endocardial infection, especially if it is long continued. Associated with this there is often seen a hemolytic anemia and acute nephritis with red blood cells and cellular casts in the urine, which make the diagnosis certain. The disease is nearly always fatal and any hope of the patient's recovery rests on the early recognition of the disease, which is probably best and earliest made by properly taken and controlled blood cultures. Recently sodium cacodylate has been used with results that lead to the hope that early cases may be greatly helped. Cyanosis is very common in congenital heart disease and may be seen in extreme grades. Anemia is important in the production of cyanosis. Polycythemia increases the tendency to cyanosis, while anemia reduces the chances of its development. The patient in this case had an anemia of severe grade of recent development on admission. While the patient had no cyanosis while in good health, its absence could not have been due to the anemia. The late urinary changes and the pathological changes in the kidneys were of interest. Hematuria has frequently been noted in subacute bacterial endocarditis, and is often considered a sign of hemorrhagic nephritis. In this case the glomerular epithelium was swollen; several glomerular loops were bloodless and disintegrated, while an active proliferation of Bowman's capsule caused crescents of swollen and

proliferating cells. No bacterial glomerular emboli were demonstrated. The absence of the emboli was unusual, as was also the absence of emboli and infarcts. In view of the numerous vegetations that were found in the heart, and their friable condition, it is impossible to explain why embolic phenomena were not present.

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## OBSTETRICS

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UNDER THE CHARGE OF

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"Once a Cæsarean Section Always a Cæsarean Section," an Untruth.—In the *American Journal of Obstetrics*, January, 1923, page 86, Greenhill quotes this axiom saying that it is not true. He reports 4 cases of women who had been delivered by Cesarean section, 1 of whom was delivered by forceps and the other 3 gave birth spontaneously. In 3 cases the uterine cavity was explored and was found normal. Where the classic section had been done a relatively thin scar was found, and in 1 patient who had the low cervical operation no trace of a scar could be discovered. In 3 of these sections catgut only was used in closing the uterus; 1 patient had contracted pelvis; another malposition of the child; another a low placenta with hemorrhage, and the fourth a breech presentation. These were the indications for the original section. In this last case, shortly after the original section, the patient again became pregnant and was spontaneously delivered after a long and tedious labor. When her third pregnancy occurred, examination found that the scar of the original section was easily felt and indicated thinning and overstretching. The patient desired sterilization and accordingly a low fundal incision was made in the uterus, followed by the delivery of the child, the excision of portions of the tubes, and the burial of the ends of the tubes in the folds of the broad ligament. These cases indicate that, as the writer states, that Cæsarean section does not mean that in a subsequent pregnancy the operation must be repeated. In the experience of the reviewer, a patient who had a classic section for accidental separation of the placenta has since given spontaneous birth to two exceptionally large and well-formed children. This has occurred in a number of cases.

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The Capillary Circulation in Eclampsia.—In the *Arch. f. Gynäkol.* (1923, 116, 443) HINSELMANN gives the result of his study in 19 cases of eclampsia. He has collected histories of 6 other cases and in addition there have been 8 additional reported, in all 33 patients suffering from eclampsia were studied to observe the changes in the capillary circulation. As was expected the capillary circulation was much disturbed in 9 out of 10 of these patients. The phenomena were

spasm of the capillaries occurring at intervals which often entirely stopped the flow of blood. Even when these attacks were not present capillary circulation was much impaired. This condition improved when the uterus was emptied. Drugs and the extracts of glands did not influence this condition but bleeding seemed to be of some service. Pregnant women in health do not entirely escape this complication, for there is occasional contraction of the capillaries in about 5 per cent. In patients showing abnormal conditions in the kidneys this condition is three times as frequent. Clinically it has long been observed that in the presence of pronounced convulsions the general circulation is greatly embarrassed and the passage of blood through the small vessels at times ceases, probably produced by substances elaborated in the placenta. There is a tendency during pregnancy to undue irritability and frequent contraction of peripheral vessels. When the uterus is emptied in healthy patients this gradually disappears and may be one of the causes for the slow pulse seen in the puerperal period. Obviously those viscera normally most rich in blood must be most affected by this condition. As it is produced by toxins it may be most completely demonstrated in those portions of the body where the circulation is very free, the vessels small in size and readily dilating and contracting, these conditions are present in the kidneys, in the skin and in the brain. The article is profusely illustrated by charts, photographs of apparatus and tables. Of this material there is an illustration of a case, severely ill and threatened with eclampsia, where the circulation was studied for a period of eight minutes, during this time the circulation of blood was stopped 63 times, and this was more than half of the entire period.

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**The Metabolism of Pregnancy.**—KNIPPING (*Arch. f. Gynäkol.*, 1923, 116, 521) has studied the action in pregnant patients of some of the glands of internal secretion. He has especially investigated the anterior portion of the pituitary gland. This he believes causes certain conditions in the metabolism of pregnant patients which develop in the last months. When reproductive life is about to cease, alterations in this portion of the gland are followed by the accumulation in the patient of fat. If his observations are accurate this may give a suggestion concerning the treatment of this condition.

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**Immunizing against Puerperal Infection.**—LOUROS (*Arch. f. Gynäkol.*, 1923, 116, 589) in the clinic at the University of Athens has endeavored to prevent streptococcus sepsis by injecting vaccines shortly before labor. His results seemed to indicate that the twentieth and tenth day before labor are the best times for this treatment and that from 250 to 500 million bacteria may be given. No failures are reported by the writer, but the interesting question arises as to how he can be positive that his method has absolutely prevented infection, when infection in cases handled with reasonable care, is comparatively infrequent.

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**The Relation between Polycythemia and Hypercholesteremia in Pregnancy.**—BENDA (*Arch. f. Gynäkol.*, 1923, 116, 506) has studied this subject and has reached conclusions which seem of particular value. Unquestionably during the last weeks of pregnancy cholesterol is increased in quantity in the patient's blood; this increase goes steadily

on until labor; by the eighth day after labor there has been a marked decrease. The red blood cells vary greatly in different patients at the end of pregnancy. The increase in the red blood cells is not the result of concentration of the blood; it is not usual to find elementary forms of red blood cells in the blood stream of pregnant patients. When polycythemia is present the quantity of cholesterin in the blood is increased; there seems to be a relation between this condition and the number of red cells. The cholesterins apparently lessen or inhibit somewhat the physiological hemolytic process in the red blood cells; this has also to do with the condition of the medulla of the bones, and the number of red blood cells during pregnancy is the result of a correlation of activity between those organs in the body which tend to produce and those which tend to destroy the red cells.

**The Effect of the Roentgen-ray upon the Ovaries and upon Impregnation and Gestation.**—LACASSAGNE and COUTARD (*Gynéc. et Obst.*, 1923, No. 1) contribute a paper upon this subject in which they describe experiments upon animals and the examination of tissues taken from these animals. From these experiments they find that irradiation of the ovaries of a rabbit, if one application is made of no great strength, still produces upon the ova a very definite lesion, this lesion has not been fully described and cannot be demonstrated by microscopical examination of the follicle; it varies in intensity with the degree of radio sensibility possessed by the different primary follicles at the moment of application and is especially pronounced when the roentgen-ray is employed just as the follicles are becoming mature. The result of this is to hinder the development of the ovum in various ways. In some instances atresia of the follicle was produced, the ovum did not become fecundated; in others, there was absence of nidation, the embryo died and fetal death resulted, and the young when born died at term or perished some weeks after birth. If one can apply the results of experiments upon animals to human beings it is fair to suppose that the roentgen-ray may produce similar results in man. Evidently the treatment of metrorrhagia in young women by the roentgen-ray should be conducted with great caution, and while it is essential to check hemorrhage, it is of more importance not to disturb the normal functions of the ovaries. The organs of the rabbit are peculiarly appropriate for such experiments because they closely resemble those of the human subject in their anatomy and physiology.

**Cervical Placentæ.**—FREUND (*Ztschr. f. Geburts.*, 1923, 85, 581) draws attention to the treatment of cervical placenta. He believes that not only is the ovum in its abnormal attachment the essential feature, but that the condition of the uterine wall is also of importance. The villi of the chorion will attach themselves to any surrounding tissues and the degree of the attachment will depend somewhat upon the character and condition of this tissue. When circumstances are favorable, the villi frequently develop in great depth, and this is especially true in cervical placenta where the villi assume an almost destructive character. That the internal os can be covered by chorionic villi seems to be demonstrable. The fact that hemorrhage begins at varying periods in labor in these cases is due to the depth of penetration of the

placental villi into the substance of the cervix. The intensity of bleeding will depend upon the depth of penetration and the abundance of the placental tissue. Cervical placenta he considers the most dangerous of all forms of placenta previa. In a series of 25 published cases the maternal mortality was 80 per cent. Bleeding often follows the first vaginal examination which should arouse suspicion of a cervical placenta. There are frequently varicose veins in the cervix and surrounding tissues which readily bleed upon examination. The writer reports the case of a primipara, aged forty-three years, in the seventh month of pregnancy who on admission to hospital was found to have two varicose veins of considerable size extending across the anterior lip of the cervix. There was a cervical placenta and the patient had suffered from hemorrhage; bimanual version was then performed but extraction was delayed. The patient rallied well from the first hemorrhage but forty-five minutes later had a sudden collapse without external bleeding. As the anemia was rapidly progressing abdominal Cæsarean section was at once performed, a seven months' dead child removed and considerable blood which had extravasated was removed from the uterus. The placenta could not be separated from the cervix and the effort to do this tore through the cervical wall so that the operator was obliged to perform total extirpation, the patient died of anemia four hours later. In the matter of treatment the writer urges that all vaginal examinations and manipulation, including the use of the tampon, be forbidden outside of hospital. He believes that the low form of section is indicated and he has had excellent results with the old classic operation as well. In the discussion, the majority of opinion favored delivery by section and agreed in emphasizing the fact that these cases must not be disturbed outside of the hospital.

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## GYNECOLOGY

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**Radium Needles in Cancer.**—Over three years of study and clinical experience with radium needles have led CLARK (*Am. Jour. Roentgen.*, 1923, 10, 204) to the recognition of the following facts concerning this form of radium application: When radium needles are introduced into neoplastic tissue the maximum reaction is obtained owing, in the first place, to the direct action of the rays upon the tissues, and in the second place, to the cross-fire effect from needle to needle. The total radiation from each needle can be utilized locally in distinction to the extravagant dissemination in the air by approxi-

mately three-fourths of the radio-activity during surface application. The corrosive action of the body fluids on the steel needles as originally provided has been largely overcome by the use of nickel alloy. In some cases, however, platinum or irido-platinum needles are more desirable although these are less durable and bend more easily. In addition to the strength of the metal employed in the composition of such needles, an important factor is its property of filtering out the beta rays or all but the hardest beta rays, depending upon the thickness and density of the metal employed. The fact that some of the beta rays are filtered out by the needle walls has been found to be of advantage, since the same therapeutic result can be obtained without as great an inflammatory reaction and after-discomfort to the patient as when all the beta rays are employed. Also, there is less danger of subsequent formation of undesirable slough. By the use of radium in needles and the judicious consideration of this property of filtration, a dose can be given which will exert a lethal action upon malignant cells without causing necrosis with sloughing, but rather a retrogression of the growth and relative conservation of the normal cellular elements. The general appearance is that of mummification, rather than the usual necrotic changes. A small quantity of radium, from 1 mgm. to 10 mgm. in each needle, can be used to even greater advantage than a larger quantity, for the reason that this greater concentration will be more likely to produce sloughing, while the desired effect is to change the character of the cells and render them innocuous by atrophy, also secure final replacement by fibrous connective tissue. Such quantities of radium in needles inserted at equidistant points throughout a growth will, by crossfire action, result in homogeneous radiation over a wide area, while a single capsule or needle containing a large quantity of radium, whether buried in the growth or applied to the surface, will exert its greatest influence at the point of contact, its effect growing rapidly less potent as the distance from the radium is increased. Dosage is all-important in radium needle application and is most difficult to estimate. Important points to be considered are: The anatomical location of the neoplasm, its type and its grade of malignancy. For example: The uterus will stand a larger radium dosage than the rectum; the breast than the buccal surface, the tongue, the floor of the mouth and the tonsil; the stomach more than the intestine, etc. The requirements of the individual case must also be studied. A correct technic is therefore of the utmost importance. With good judgment and such technic, most gratifying results will often be obtained, but should mistakes be made in any of these several factors much damage and suffering may result. For example, too small a dose may only stimulate the neoplasm, while an overdose may result in such dense fibrosis that circulation in the mass is totally arrested. Then within a few weeks or months sloughing will occur, resulting in an ulcer which will not heal. This condition is as bad, though benign, as the one originally present. It has been Clark's experience that needles containing 10 mgm. of radium should not be inserted into a malignant growth at a distance greater than 25 mm. apart, as a lethal effect, from this standpoint, will not be produced beyond this distance. In some instances the distance should be even less, depending upon the degree of radiation concentration desired, the exact amount of radium in each needle, and also the time



allotted for the treatment. Needles with cutting trocar points have been found to be more generally useful than those with round tapering points. A trocar is used before the insertion of a needle if the tissue is dense, but if of soft consistency, the needle may be inserted directly into the tissue. The secondary radiation from metal in contact with the tissues beneath the surface does not produce such an acute reaction as does contact of the metal upon the skin surface. The patient should be prepared as for any surgical operation, since infection may occur if the field is not sterile. The needles may be inserted, as a rule, under local anesthesia. Where, however, many needles are to be employed, or there is any other contraindication to the use of local anesthesia, such as a supersensitive or nervous patient, general anesthesia may be induced.

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## PATHOLOGY AND BACTERIOLOGY

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**Experimental Gangrene.**—The majority of attempts to produce gangrene in animals with spirochetes and fusiform bacilli have failed. Since it is commonly accepted that gangrenous necrosis occurs only in tissue previously devitalized, KLINE (*Jour. Infect. Dis.*, 1923, 32, 481) conducted a series of observations on guinea-pigs by inoculating material containing spirochetes and fusiform bacilli into the hind extremities, one of which had been previously traumatized by repeated clamping with a hemostat. By this procedure, he was able to obtain gangrenous necrosis on the injured side in 78 per cent of cases. The experiments included 62 animals. In one group, material from pulmonary gangrene containing innumerable spirochetes, fusiform bacilli and other bacteria was passed from guinea-pig to guinea-pig producing typical gangrene in the thirty-sixth generation. In another group similar material was injected into 2 guinea-pigs in the routine manner and into 1 rabbit intrabronchially. From the same case material from a carious tooth showing organisms similar to those in the gangrenous lung was injected also in 2 guinea-pigs in the usual manner and into 1 rabbit intrabronchially. All the guinea-pigs showed marked gangrenous necrosis on the traumatized side and the rabbits, dying in nine days, showed extensive gangrenous pleuropulmonary lesions. In a third group, material from 4 cases of Vincent's angina containing spirochetes and fusiform bacilli was injected in the routine manner into 4 guinea-pigs, resulting in typical gangrene in 3. The author concludes that "the experimental production in the rabbit of pulmonary gangrene with material from a carious tooth containing spirochetes and fusiform

bacilli is further evidence that the aspiration of these organisms from lesions in the mouth of human beings may lead to pulmonary gangrene."

**A Bacteriological Study of Vulvo-vaginitis of Children.**—Vulvo-vaginitis in girls of school age leads to exclusion from school, based on the belief that the infection is gonorrheal. In order to ascertain the bacteriological flora of this condition, ANDERSON, SCHULTZ and STEIN (*Jour. Infect. Dis.*, 1923, 32, 444) made a detailed bacteriological study of 42 school girls up to fifteen years of age with inflammation about the vulva. Direct smears, cultures and immunological reactions comprised the technic. Of the 42 cases, 35.7 per cent were found to be due to the gonococcus and 64.3 per cent were non-specific. In 53.3 per cent of the specific cases the gonococcus was isolated in pure culture, while in the remainder the specific diagnosis was based on the presence within leukocytes of morphologically typical, Gram-negative diplococci, indicating that the direct smear examination should be given preference over the cultural method as a diagnostic procedure. It was impossible by immunological methods to differentiate the gonococci isolated from children from those derived from women. In the non-gonorrheal cases a mixed flora was present, but streptococci of intestinal origin appeared to be the most important agents. Staphylococci, colon bacilli and Gram-positive bacilli were encountered frequently. The authors believe that uncleanliness and local irritation are the important, and probably the primary, factor in the non-specific cases, which were more amenable to therapeutic measures than the gonorrheal cases. They believe, also, that quarantine and exclusion from school are not necessary in the non-gonorrheal cases.

**Studies in the Nature of Bacillus Acidophilus Therapy.**—In order to study the influence of chemical and physical factors, KOPELOFF and BEERMAN (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, No. 8, 425) centrifuged *B. acidophilus* milk and filtered it through a Mandler diatomaceous candle, thus altering its chemical constituents but little. When fed to constipated patients it was practically without effect. Regular *B. acidophilus* milk ingested subsequently resulted in an increase in the number of normal defecations. When *B. acidophilus* milk was sterilized and lactic acid added, thus approximating the original chemical composition, and when fed to constipated patients, little change was noted. The authors believe that these data indicate that *B. acidophilus* therapy is essentially bacteriological rather than physical or chemical in nature.

**The Presence of Bacteria in the Lungs of Mice Following Inhalation.**—As considerable discussion has arisen at various times as to whether inspired bacteria reach the lungs or are filtered out in the nasal passages, STILLMAN (*Jour. Exper. Med.*, 1923, 38, 117) conducted a number of experiments on mice in the hope of obtaining further information concerning pulmonary infection under normal conditions. The mice were allowed to inhale an atmosphere in which a fine mist had been produced by spraying a culture of organisms to be studied. As a rule the mice were removed from the spray box one hour after spraying and were killed at various intervals, cultures being made in broth from the lungs,

heart's blood and spleen. The total number of mice exposed to a spray containing virulent hemolytic streptococci was 45, those exposed to a spray containing influenza bacilli was 32 and those exposed, similarly, to staphylococci was 10. It was found that the bacteria, under the conditions of experimentation, readily penetrated into the lower respiratory tract. Pneumococci usually disappeared within a few hours and gave rise to no infection. Hemolytic streptococci, on the other hand, persisted in the lung for a considerably longer time and a general septicemia usually followed. Attempts to determine the conditions under which pneumococci which have reached the lung by inhalation may induce a local or general infection were not successful.

**Experimental Production of Streptococcus Endocarditis with Glomerular Nephritis.**—Recognizing the extremely high mortality in human subacute streptococcus endocarditis and that the mechanism of production of this disease in human beings depends on two constant factors—injury to the valve with subsequent infection, KINSELLA and SHERBURNE (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 252) were able to produce a bacterial endocarditis and glomerular nephritis in dogs by injuring the aortic valve by inserting an appropriate instrument into the left carotid and, after recovery, injecting green streptococci intravenously. The bacterial vegetations on the aortic valve leaflets were identical with those encountered in human patients. Only those dogs which lived longer than fourteen days showed the glomerular lesion, which consisted of a partial thrombosis of the tuft with hyaline degeneration, hemorrhage and polymorphonuclear leukocytic infiltration. The authors believe that they “have reproduced a bacterial infectious disease which is of sufficient duration to permit thorough study of many of the unknown factors of infection and immunity.”

**The Susceptibility of Cells to Radium Radiations.**—As shown by experiments with paramecium and other protozoa, the response of cells to radium radiations is influenced by the temperature of the cells at the time of radiation and the permeability of the cell membrane. PACKARD (*Proc. Soc. Exper. Biol. and Med.*, 1923, 20, 226) exposed paramecia, which were descendants of a single wild cell, to radium, amounting to 13.4 mg. of element. The radium was enclosed in a thin-walled glass capsule, and was held at a distance of 2 mm. from the water containing the cells. It was found that cells were more susceptible to radiations at the upper limit of their physiological range of temperature than at their lower limit. At 14° C. the lethal dose was about ten hours; at 37° C. it was one and a half hours. For each rise of 8° C. the length of the lethal dose was halved. The curve expressing these relations was the same as that which expressed the relation between temperature and rate of metabolism in paramecium as shown by the rapidity of cell division and of the pulsation of the vacuoles. Cells whose membranes are relatively permeable were more susceptible to radiations than those whose membranes were relatively impermeable, as determined by the rate at which dilute  $\text{NH}_4\text{OH}$  entered the cells and decolorized the neutral red by which they were stained. Radiation increased the permeability of the cells by injuring the cell wall. If the treatment were continued long enough the cells cytolyzed

completely. "From this it follows that when cells are already highly permeable as they are during growth and division, complete cytolysis quickly ensues; whereas when the cell membrane is relatively impermeable, as it is in resting cells, radiation must be long continued before destructive cytolysis can be observed."

**Intestinal Flora in Diarrhea.**—"It is generally recognized that the feeding of grain foods and other carbohydrates, particularly lactose and dextrin, to normal animals favors a predominance of aciduric bacteria in the feces, while the feeding of animal proteins favors the development of proteolytic organisms." By applying methods used by others in studying the effects of diet on the fecal flora, HINES (*Jour. Infect. Dis.*, 1923, 32, 280) ascertained the flora of the feces from 10 normal persons, from 8 individuals with evidence of organic lesions in the intestinal canal and in 9 with diarrhea, 3 of whom were diagnosed "fermentative diarrhea." The proportion of aciduric bacteria to proteolytic ones was determined by the method of Cannon—the so-called colon-acidophilus ratio. Particular attention was paid to *B. Welchii*. It was found that the fecal flora of all normal stools was proteolytic in type and that the spores of *B. welchii* were present in 9 of 10 cases. In the 8 cases who had diarrhea as a result of intestinal lesions, ulcerative or otherwise, the findings were very similar and differed in no way from those of normal stools, other than a definite increase of *B. welchii* spores. On the other hand 2 cases of "fermentative diarrhea" yielded an aciduric flora, whereas a third similar case was proteolytic in character. Spores of *B. welchii* abounded in stools with a proteolytic flora and were absent in those with an aciduric flora.

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## HYGIENE AND PUBLIC HEALTH

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**Tuberculosis: Its Predisposing Causes.**—SMITH (*Public Health Reports*, 1923, 38, 777) shows the danger of infection in childhood and urges that children should be kept away from acute cases of the disease. It is stated that over 1,000,000 people in the United States are constantly sick with tuberculosis and some "carriers" exist. The almost universal infection of people is mentioned, weakened resistance, lack of proper food, exhaustion, bad air, influence of occupation, race, climate, age, predisposing diseases, and alcohol and tobacco are appraised and the following summary given: At an early age practi-

cally all people have become slightly infected with living tubercle bacilli. This fact need not cause alarm, because it probably gives a slight degree of protection against a subsequent infection. Safety, however, depends on the maintenance of a high degree of body resistance to prevent these latent bacilli from producing active tuberculosis. This is not to be accomplished by becoming an athlete, but by the daily observance of general hygienic principles throughout life. Keep the body well nourished, avoid great fatigue, work and sleep in well-ventilated rooms, in freely flowing air and spend as much time as possible outdoors; but carefully reserve hours for adequate rest, as well as for recreation, practise deep breathing and proper carriage, avoid other diseases as far as possible, and be temperate in all things.

**The Prevention of Simple Goiter.**—KIMBALL (*Public Health Reports*, 1923, 38, 877) gives briefly the distribution of goiter in various parts of the world, then discusses the relation of iodine deficiency to the disease, after which data in the shape of figures and diagrams are presented to show the benefits that may be expected from the systemic use of iodine, conducing with the following summary: In these endemic goiter districts, if every woman would keep her thyroid saturated with iodine during every pregnancy she would not develop goiter, nor would there be any tendency toward goiter formation in the thyroid of her child. This would save two of the goiter periods in the life of any woman. Then, if every girl would keep her thyroid saturated with iodine during adolescence, that is, from the age of eleven to sixteen years inclusive, none would develop goiter. As to the prevalence of goiter in boys, the following facts are pertinent: (1) Goiter is at least six times more frequent in girls than in boys. (2) A large majority of goiters in boys are congenital and could be prevented by the administration of iodine to the mother during pregnancy. (3) While occasionally a boy does develop goiter at puberty, or after illness, or as the result of some chronic infection, in most cases the goiter will disappear if it is treated promptly and properly. We feel, therefore, that the maximum good from a minimum effort would be gained by applying the principle of goiter prevention to girls as a public health measure. This can best be done through our public school organization; and the education on this subject will ensure application of this method of goiter prevention in later life. The prevention of goiter during pregnancy necessarily depends on the medical profession and on the education of the people as a whole. Each family physician and obstetrician should make this an important part of the routine care of every patient; and the diffusion of this knowledge must be such that each expectant mother will anticipate such care.

**Biological Evidence for the Inheritability of Cancer in Man.**—SLYE (*Jour. Cancer Res.*, 1923, 7, 107) states that cancer and non-cancer tendencies segregate out and are transmitted as such. They are therefore unit characters. A specificity of tissue type in specific organs from ancestor to offspring segregates out and is transmitted as such. It is therefore a unit character. Since these things are unit characters, it is possible to manipulate them by selective breeding and thereby to implant them indelibly in any species or to eliminate them perma-

nently and completely from any species. Cancer and non-cancer behave like the absence and presence respectively of a mechanism fitted to control proliferation and differentiation in regenerative processes, and an animal either has this mechanism or lacks it, no matter to what species he may belong. There is therefore a ready and certain genetic method of escape from cancer for the individual and for the race. The demonstration of the inheritability of cancer and non-cancer tendencies in mice is a demonstration of the inheritability of these tendencies in man and in all other species which show cancer, if we are to maintain the theory of evolution and to admit that there is such a thing as biological law. The study of a cancer behavior, which has demonstrated itself to be fundamentally a biological problem, makes evident the necessity of understanding and considering the biological facts underlying all pathological conditions. And, therefore, when we have properly placed biology under all our pathology and bacteriology, all our physiology and therapy, there will no longer be these monstrous diseases, but only the slow and natural death which is the fatigue and diminution and final cessation of the organ and the organism. From the procedure of analyzing stock into its unit characters in order to manipulate cancer tendency, there has emerged the fundamental law of heredity. What goes into the germ plasm must come out in the offspring.

**Vincent's Angina and Noma. Experimental Gangrene.**—KLINE (*Jour. Inf. Dis.*, 1923, 32, 481) points out that the majority of attempts to produce gangrene in animals with spirochetes and fusiform bacilli have failed. Veszpremi believes that when the viability of tissue is diminished by disease, the organisms living in the neighborhood, including *Spirochæta gracili*, increase enormously in number. There is also an increase in the virulence of the organisms and the process takes on a progressive character with the penetration of spirochetes into the tissue prepared for it. The spirochetes are aided by the fusiform bacilli, and under the influence of the cladothrix and other bacteria the characteristic foul-smelling gangrene follows. Since it is commonly accepted that gangrenous necrosis occurs only in tissue previously devitalized, it was decided to traumatize tissue before inoculating the material containing spirochetes and fusiform bacilli. Kline states that in the presence of devitalized tissue, gangrene may be produced in guinea-pigs with material from dental caries and pyorrhea alveolaris, Vincent's angina and pulmonary gangrene containing spirochetes and fusiform bacilli. The experimental production in the rabbit of pulmonary gangrene with material from a carious tooth containing spirochetes and fusiform bacilli is further evidence that the aspiration of these organisms from lesions in the mouths of human beings may lead to pulmonary gangrene.

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